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LYCOPODIUM ALKALOIDS

IV. REACTIONS OF α-CYANOBROMOLYCOPODINE AND ITS DERIVATIVES[1]

BY L. R. C. BARCLAY[2] AND DAVID B. MACLEAN

ABSTRACT

The hydrogenolysis and hydrolysis of α-cyanobromolycopodine to the secondary tricyclic base, α-des-dihydrolycopodine, is reported. The latter compound was converted to the methiodide in poor yield so that further degradations of the molecule through this derivative were not feasible. Hydride reductions of α-cyanobromolycopodine and some of its derivatives are recorded. The presence of a methylene group adjacent to the carbonyl group in lycopodine has been proved. Evidence is presented which suggests that the carbonyl group and the nitrogen atom are relatively close to one another in the molecule.

In a previous communication, MacLean, Manske, and Marion (4) reported the reaction of lycopodine with cyanogen bromide. They isolated two isomeric cleavage products, designated α- and β-cyanobromolycopodine. The α-isomer was formed in predominant amount. A number of reactions of these compounds were studied and from their work it was found that α-cyanobromolycopodine was a primary bromide.

In this investigation the study of the reactions of α-cyanobromolycopodine was extended in the expectation that more information concerning the ring structure of the alkaloid would be obtained. In this respect our work has been only moderately successful, but a number of new derivatives of interest for further study have been prepared.

Lycopodine was isolated from the crude mixed alkaloids from several plant sources by a convenient procedure outlined in the experimental section. The procedure for conversion to the isomeric cyanobromides has also been improved and reported. α-Cyanobromolycopodine, the major product, was converted to α-cyanolycopodine by the method reported previously (4). Hydrolysis of α-cyanolycopodine, $C_{17}H_{26}ON_2$, yielded the secondary base α-des-dihydrolycopodine, $C_{16}H_{27}ON$, which showed absorption in the =NH region of the infrared spectrum. This secondary base was acylated with acetic anhydride to a neutral amorphous compound which no longer showed =NH absorption but had a band at 1640 $cm.^{-1}$ in the amide region of the infrared. It was also methylated by formaldehyde and formic acid to a tertiary base

[1]*Manuscript received June 22, 1956.*
Contribution from the Department of Chemistry, Hamilton College, McMaster University, Hamilton, Ontario.
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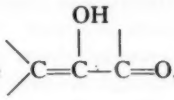
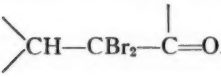
which analyzed for a single $=N—CH_3$ group. Conversion of the tertiary base to the quaternary salt by methyl iodide proceeded in very poor yield. An attempt to carry out a reductive fission of the quaternary salt was not successful. Other degradations of the methiodide were not attempted because of the low over-all yields obtained in the conversion of α-cyanolycopodine to the methiodide. No satisfactory explanation can be offered for the failure of the secondary base to alkylate readily with alkyl halides nor of the tertiary N-methyl base to form a methiodide readily. Lycopodine, on the other hand, formed a methiodide rapidly and quantitatively when an acetone solution of the base was mixed with methyl iodide.

A number of hydride reductions were carried out on α-cyanobromolycopodine and its derivatives to prepare compounds for dehydrogenation and other degradation studies now in progress. The secondary base, $C_{16}H_{27}ON$, was converted to the corresponding carbinol, $C_{16}H_{29}ON$, by lithium aluminum hydride. An alternative and more convenient preparation of this carbinol resulted from the direct reduction of α-cyanobromolycopodine with lithium aluminum hydride. In this conversion the bromine underwent hydrogenolysis, the carbonyl group was reduced, and the $=N—CN$ linkage was converted to $=NH$. Some neutral material was also derived as a by-product of this reduction in which the $=N—CN$ grouping was still present. This material proved to be the corresponding cyanamide, $C_{17}H_{28}ON_2$, which was also derived by two alternative procedures. The Meerwein–Ponndorf reduction of α-cyanolycopodine was slow and inefficient, but reduction of α-cyanobromolycopodine with sodium borohydride proceeded readily to give a good yield of the compound $C_{17}H_{28}ON_2$.

The displacement of bromine by hydrogen in the sodium borohydride reduction is somewhat unusual since this reagent does not ordinarily affect carbon–halogen linkages under these mild conditions. Since the reaction has been carried out several times with the same result, it would appear that this is an authentic case of a sodium borohydride reduction of an aliphatic halogen.

The bromination of α-cyanolycopodine was studied in an attempt to prepare derivatives of the compound suitable for oxidative degradation. In carbon tetrachloride solution α-cyanolycopodine readily consumed bromine with deposition of a solid amorphous precipitate. From this precipitate it was possible to isolate, although in low yield, a monobromo derivative. The carbonyl absorption in the infrared of this brominated derivative was displaced by 10 $cm.^{-1}$ to 1710 $cm.^{-1}$ in comparison to the starting material at 1700 $cm.^{-1}$. Such a shift is consistent for an α-bromoketone (1). In contact with water or aqueous alkali this product readily lost its bromine to produce a mixture of compounds probably alcoholic and olefinic in nature.

The main product of the bromination reaction was amorphous, and despite repeated attempts, it could not be induced to crystallize. In common with the monobrominated compound it readily lost its bromine in contact with aqueous alkali. Treatment of these amorphous residues with alkaline aqueous dioxane yielded a product from which a crystalline derivative was obtained.

This compound, which analyzed for $C_{17}H_{24}O_2N_2$, had the properties of an enol. The infrared spectrum indicated the presence of a conjugated carbonyl group, an olefinic double bond, and an hydroxyl group. The ultraviolet absorption spectrum showed strong absorption at 2800 Å which is indicative of an hydroxylated α,β-unsaturated carbonyl chromophore (3). The analytical and spectral results suggested a structure of the following type  . Such a structure would arise from an α,α-dibrominated ketone,  . The bromination reaction thus proceeded to give a mixture of mono- and di-brominated ketone.

The failure of lycopodine to form a benzal derivative (2) is at variance with the above results and we considered them suspect for this reason. However, α-cyanolycopodine formed a monobenzal derivative, $C_{24}H_{30}ON_2$, and the presence of a methylene group adjacent to the carbonyl group was confirmed. Under similar conditions, lycopodine failed to react in confirmation of the work of Douglas *et al.* quoted above. One must therefore conclude that this methylene group occupied a hindered position in lycopodine and the hindrance was relieved on ring fission in the formation of α-cyanolycopodine.

The ease with which α-cyanolycopodine brominated led us to investigate the bromination of lycopodine and α-des-dihydrolycopodine. Both the bases readily formed monobromo derivatives isolated as their hydrobromides. Both of these brominated hydrobromides underwent decomposition on conversion to the free bases and no identifiable fragments could be isolated from either substance. Since both these compounds gave a Fehling's test, they are undoubtedly α-bromoketones. The pK_a of these bromo compounds was determined and compared with the parent bases and the dihydro bases. These results are summarized below:

lycopodine	9.06
dihydrolycopodine	9.2(2)
bromolycopodine	7.30
α-des-dihydrolycopodine	9.05
α-des-tetrahydrolycopodine	9.80
bromo-α-des-dihydrolycopodine	7.20

The similarity in pK_a of lycopodine and α-des-dihydrolycopodine suggests that in the ring fission reaction the relationship of the nitrogen and carbonyl groups has not been altered. The increase in pK_a on reduction of these compounds is probably not significant. However, the greatly decreased basicity of the brominated bases implies a rather close proximity of the carbonyl and nitrogen atoms in the molecule.

EXPERIMENTAL

Lycopodine

Three plant species, *L. clavatum*, *L. obscurum*, and *L. tristachyum*, were used as a source of lycopodine. The plant materials were extracted by the method of Manske and Marion (5). In all cases lycopodine was derived from the crude alkaloids of these plant extracts by chromatography on alumina using chloroform as eluant. Lycopodine passed rapidly through the column and was thus separated from other alkaloid constituents. Final purification was achieved through conversion to the perchlorate.

The pK_a of lycopodine was determined by the titration of the perchlorate and the hydrobromide in 50% methanol–water. Values obtained were 9.06 and 9.07, respectively.

Reaction of Lycopodine with Cyanogen Bromide

Lycopodine (15 gm.) dissolved in 150 ml. of dry benzene was added over a period of 10 hr. with stirring to a solution of 50 gm. of cyanogen bromide in 150 ml. of dry benzene. The reaction mixture was then allowed to stand overnight. The benzene and the excess cyanogen bromide were removed under vacuum. The residue was taken up in chloroform, washed with dilute acid, water, and dilute sodium bicarbonate. The acidic and aqueous washings were saved and 1.2 gm. lycopodine was reclaimed therefrom. The chloroform solution was concentrated and adsorbed on a column of alumina. Elution with chloroform yielded a first fraction of cyanobromides (18.9 gm.) which crystallized in contact with ether. Following the cyanobromides down the column was a distinct brown band which yielded an amorphous residue. This residue showed strong absorption in the hydroxyl region as well as the carbonyl and nitrile region. This residue (1.0 gm.), on acetylation, yielded a crystalline O-acetyl derivative identical to α-cyanoacetoxylycopodine reported previously (4).

The cyanobromide residues were crystallized from ether. The first crop of crystals consisted of pure α-cyanobromolycopodine, m.p. 140–141°.[3] Yield = 8.8 gm. Concentration of the mother liquors yielded crystalline material which melted over a wide range and was a mixture of the α- and β-cyanobromides. By repeated recrystallizations it was possible to isolate additional crops of the pure α- and in some cases the pure β-isomer, although these cases were rare and perhaps fortuitous. Pure β-isomer was obtained in many cases by manual separation of the crystals, which have distinctly different forms; the α-isomer crystallized in pyramidal form, the β-isomer in needles. Fortunately it was possible to convert this mixture into separable derivatives of use in other investigations under way in these laboratories. The pure β-cyanobromolycopodine melted at 106–108°.

Both isomers exhibit strong absorption in the infrared[4] at 1700 cm.$^{-1}$ in the carbonyl region and at 2200 cm.$^{-1}$ in the —C≡N region. There are distinct differences in the 600–1200 cm.$^{-1}$ region.

[3]*All melting points are corrected.*

[4]*Infrared spectra were carried out in nujol mull unless otherwise specified and were determined on a Perkin-Elmer No. 21 recording spectrophotometer with a sodium chloride prism.*

Hydrolysis of α-Cyanolycopodine

α-Cyanolycopodine (0.5 gm.), prepared by the method of MacLean, Manske, and Marion (4), was refluxed overnight with 20 ml. of 2 *M* hydrochloric acid containing 5 ml. of *n*-propanol to ensure partial solution. The clear solution, concentrated to remove the alcohol, deposited crystals of the hydrochloride upon cooling. After recrystallization from methanol, the hydrochloride melted above 300°.

Calc. for $C_{16}H_{27}ON.HCl$: C, 67.23; H, 9.81; N, 4.90.
Found: C, 66.88, 66.92; H, 9.76, 9.78; N, 4.84, 4.72%.
pK_a (50% methanol–water) = 9.05.

The free base, obtained from the hydrochloride, was a solid, difficult to obtain in pure form, which softened at 45° and melted at 49° after repeated crystallizations from hexane. Its infrared absorption spectrum contained no bands in the nitrile region, but had the usual carbonyl band at 1694 cm.$^{-1}$ and a strong band at 3330 cm.$^{-1}$, indicative of an =NH grouping.

Reaction of α-Des-dihydrolycopodine with Acetic Anhydride

α-Des-dihydrolycopodine (0.1 gm.) was dissolved in a few cubic centimeters of acetic anhydride and the solution heated on the steam cone in the presence of anhydrous sodium acetate. After removal of excess acetic anhydride under vacuum, the residue was treated with ether and the ether solution washed with dilute hydrochloric acid, sodium bicarbonate, and water. Upon distillation of the ether there remained an amorphous solid. This material did not crystallize from the usual solvents. However, the infrared absorption spectrum contained a strong band at 1640 cm.$^{-1}$ which, together with the absence of absorption in the =N—H region, is indicative of an acetyl derivative. The usual carbonyl band appeared at 1700 cm.$^{-1}$.

Alkylation of α-Des-dihydrolycopodine

A mixture of α-des-dihydrolycopodine (0.79 gm.), formic acid (0.16 cc., 90%), and formaldehyde (0.9 cc.) was heated under reflux on the steam bath for 10 hr. The initial reaction, which was vigorous and accompanied with foaming, subsided after one to two hours. At the end of the reaction time the mixture was diluted with water, made strongly acid with hydrochloric acid, and extracted with ether. The aqueous layer was separated, made alkaline with ammonia, and extracted several times with ether. Distillation of the ether yielded a viscous oil with no absorption in the 3300–3400 cm.$^{-1}$ region, indicative of transformation of the secondary α-des-dihydrolycopodine to a tertiary base. The carbonyl band was not shifted.

This tertiary base was dissolved in a small volume of acetone and treated with concentrated hydrochloric acid, which initiated immediate crystallization of the hydrochloride as near colorless prisms, m.p. 254°. Recrystallization from acetone yielded prisms, m.p. 256°. Yield = 0.52 gm.

Calc. for $C_{17}H_{29}ON.HCl.H_2O$: C, 64.22; H, 10.14; N, 4.20; NCH_3, 9.14.
Found: C, 64.49, 63.84; H, 9.94, 9.91; N, 4.65, 4.84; NCH_3, 9.55, 9.65.

Alkylation of α-des-dihydrolycopodine with methyl iodide and methyl

sulphate was not satisfactory, nor would the base react with butyl bromide in a sealed tube at 150°.

Methiodide of the Tertiary Base

A sample of the tertiary base (0.33 gm.) was added to excess methyl iodide and the solution refluxed on the steam bath. After about three hours a small yield of crystals was obtained. After further refluxing for 20 hr., more crystals formed, but the total yield was very low—approximately 10%. Recrystallization of the combined lots of crystals from a mixture of methanol and ethyl acetate produced colorless crystals, m.p. 192.5°.

Calc. for $C_{18}H_{32}ONI$: C, 53.33; H, 7.96; N, 3.46.

Found: C, 53.43, 53.30; H, 8.12, 7.95; N, 3.24, 3.14.

A small sample of the methiodide was dissolved in methanol, platinum oxide was added, and the mixture treated with hydrogen at 40 p.s.i.g. for eight hours. The unreacted methiodide was recovered on removal of the methanol and addition of ethyl acetate to the residue.

Lithium Aluminum Hydride Reduction of α-Des-dihydrolycopodine

Lithium aluminum hydride (1.0 gm.) was added to anhydrous ether in a three-necked flask fitted with a reflux condenser and dropping funnel, and the mixture refluxed for three hours. A solution of the α-des-dihydrolycopodine (3.0 gm.) in anhydrous ether was then added over a one-hour period with vigorous stirring. The mixture was stirred for an additional two hours before decomposition—first with moist ether, then with water. The ether layer was separated and distillation of the ether produced a crystalline product (2.0 gm., 66%). Recrystallization from ether yielded colorless crystals, m.p. 168–169°.

Calc. for $C_{16}H_{29}ON$: C, 76.43; H, 11.63; N, 5.58.

Found: C, 76.15, 76.05; H, 11.67, 11.55; N, 5.75, 5.79.

pK_a (50% methanol–water) = 9.80.

The infrared spectrum of this compound showed absorption at 3150 $cm.^{-1}$ and no carbonyl absorption.

Lithium Aluminum Hydride Reduction of α-Cyanobromolycopodine

An ethereal solution of α-cyanobromolycopodine (3.0 gm.) was added slowly with stirring to 200 cc. of ether containing 22 cc. of approximately 0.1% lithium aluminum hydride solution. The stirring and refluxing was continued for eight hours, and after the reaction mixture had been left for 14 hr., it was decomposed with moist ether. The ether layer was extracted repeatedly with dilute hydrochloric acid to remove the basic fraction. A small amount of non-basic material (0.18 gm.) was isolated on evaporation of the ether. A portion of this non-basic material was similar to the Meerwein–Ponndorf reduction product of α-cyanolycopodine reported below.

The above hydrochloric acid extract was made alkaline with ammonia and extracted repeatedly with ether and finally with chloroform in a continuous extractor. Removal of the ether–chloroform solvent left a crystalline residue (1.75 gm., 82%). Recrystallization from ether produced colorless crystals, m.p. 168–169°, which did not depress the melting point of the alcohol formed on lithium aluminum hydride reduction of α-des-dihydrolycopodine.

Reaction of α-Cyanolycopodine with Aluminum Isopropoxide

α-Cyanolycopodine (0.62 gm.) was dissolved in dry isopropyl alcohol, freshly prepared aluminum isopropoxide (2 gm.) was added, and the solution heated under reflux. The top of the reflux condenser was fitted with a trap containing a side arm with a stopcock and a cold finger filled with ethanol. The cold finger served to condense most of the refluxing isopropyl alcohol so that the distillation of the solvent along with any acetone formed was carried out at a slow, constant rate.

After several days the reaction mixture was worked up to yield a semi-crystalline residue. On addition of ether, immediate separation of colorless crystals occurred. After recrystallization from ether they melted at 191–192°.

Calc. for $C_{17}H_{28}ON_2$: C, 73.87; H, 10.21; N, 10.1.
Found: C, 73.84, 73.67; H, 9.77, 10.15; N, 8.99, 9.05.

Reaction of α-Cyanobromolycopodine with Sodium Borohydride

A solution of α-cyanobromolycopodine (4.0 gm.) in ethanol was added with stirring to a warm solution of sodium borohydride (6.0 gm.) in ethanol. After the mixture had been allowed to stand for one day, the excess sodium borohydride was destroyed with formaldehyde. The mixture was made just acid with hydrochloric acid, the solvent removed under vacuum, and the residue was extracted with chloroform. The chloroform extract was washed with dilute acid, sodium bicarbonate, and water. Evaporation of the chloroform yielded a crystalline product (3.0 gm., 97%) which was identical by mixed melting point and infrared spectrum to the product prepared by the reduction of α-cyanolycopodine with aluminum isopropoxide.

Reaction of α-Cyanolycopodine with Bromine in Carbon Tetrachloride

α-Cyanolycopodine (0.72 gm.) was dissolved in dry carbon tetrachloride in a three-necked flask provided with a stirrer and dropping funnel. Bromine (5%) in carbon tetrachloride was added slowly with stirring. After a few minutes the uptake of bromine was rapid and precipitation occurred. A total of 8 cc. of the bromine solution was added. At the end of the reaction a portion of the yellow precipitate was separated by filtration. This material rapidly became amorphous on being left to stand, and attempts to crystallize it from various solvents were unsuccessful. Chloroform was added to make a clear solution and the excess bromine destroyed by washing with bisulphite solution. Removal of the solvent under vacuum left an amorphous residue from which a crystalline product (0.17 gm.) separated on the addition of ether. Recrystallization from an acetone–ether mixture yielded colorless crystals which began to decompose at 122° and melted at 129°.

Calc. for $C_{17}H_{25}ON_2Br$: C, 57.79; H, 7.14; N, 7.94; Br, 22.6.
Found: C, 58.16, 57.99; H, 7.29, 7.16; N, 7.90, 7.82; Br, 21.8, 22.0.

The infrared spectrum of this brominated compound showed absorption in the nitrile region at 2210 $cm.^{-1}$ and the carbonyl region at 1710 $cm.^{-1}$, while the starting material had carbonyl absorption at 1700 $cm.^{-1}$.

Upon distillation of the solvent from the mother liquor of the above bromo compound, there was obtained 0.74 gm. of amorphous residue. The infrared

spectrum of this residue showed weak bands at 3400 cm.$^{-1}$ and 1630 cm.$^{-1}$ in addition to the bands at 1710 cm.$^{-1}$ and 2210 cm.$^{-1}$ for the crystalline bromo compound.

The crystalline monobromo compound reacted readily with aqueous alkali and silver oxide to yield a mixture of products. Examination of the mixture in the infrared indicated the presence of hydroxyl and conjugated carbonyl groups.

The Action of Alkali in Aqueous Dioxane on Crude Bromination Product

The non-crystalline bromination product (0.6 gm.) was heated on the steam bath in 5% potassium hydroxide containing some purified dioxane to cause partial solution. The reaction mixture soon became very dark in color and the heating was discontinued. The mixture was concentrated under vacuum to remove the dioxane and then extracted with ether. The ether extract was washed with water, acid, and alkali to yield only 0.13 gm. of non-crystalline product which was not further investigated. The aqueous layer was therefore acidified and chloroform extracted to yield a crystalline product (0.2 gm.) which melted at 157–158° after recrystallization from ether – petroleum ether.

Calc. for $C_{17}H_{24}O_2N_2$: C, 70.79; H, 8.39; N, 9.71.

Found: C, 70.76, 70.69; H, 8.35, 8.32; N, 9.25, 9.35.

The infrared spectrum of this compound had bands at 1640 cm.$^{-1}$, 1660 cm.$^{-1}$, 2210 cm.$^{-1}$, and 3340 cm.$^{-1}$. The ultraviolet spectrum showed λ_{max} = 2800 Å, log ϵ = 4. The compound gave a deep blue coloration with ferric chloride in aqueous ethanol.

Bromination of Lycopodine

A solution of 1.00 gm. of lycopodine was added with vigorous stirring to an equimolar amount of bromine dissolved in carbon tetrachloride. The uptake of bromine was very rapid at room temperature and enough additional solvent was added to redissolve the hydrobromide salt which initially precipitated.

The reaction mixture was allowed to stand overnight and the solvent removed under vacuum on the steam cone to produce a theoretical yield of bromolycopodinehydrobromide. Recrystallization from acetone–methanol yielded colorless crystals which melted at 290–295° (dec.).

Calc. for $C_{16}H_{24}ONBr.HBr$: C, 47.20; H, 6.19; N, 3.44; Br, 39.2.

Found: C, 48.64, 48.64; H, 6.25, 6.32; N, 3.67, 3.53; Br, 37.3, 37.2.

The pK_a of this bromolycopodinehydrobromide determined in 50% methanol–water medium was 7.30. The infrared spectrum showed absorption in the amine salt region 2500 to 2700 cm.$^{-1}$. The carbonyl band was at 1710 cm.$^{-1}$.

Although this bromination product of lycopodine formed readily and in good yield, attempts to convert it to the free base or to displace the substituted bromine through reactions with silver oxide or potassium acetate, and alkaline or acid hydrolysis, did not lead to any identifiable product.

Bromination of α-Des-dihydrolycopodine

α-Des-dihydrolycopodine (0.50 gm.) was treated with bromine under conditions similar to those for lycopodine. After removal of the solvent under

vacuum, there remained a quantitative yield of partly crystalline bromohydrobromide salt. Recrystallization from methanol yielded colorless needles, m.p. 275–280° (dec.).

Calc. for $C_{16}H_{26}ONBr.HBr$: C, 46.95; H, 6.66; N, 3.42; Br, 39.2.
Found: C, 46.70, 47.51; H, 7.10, 7.04; N, 3.54, 3.55; Br, 37.6, 38.1.
pK_a (50% methanol–water) = 7.20.

The infrared spectrum in nujol exhibited absorption in the carbonyl region at 1713 cm.$^{-1}$. There was a strong band at 1585 cm.$^{-1}$ attributed to the ionized salt of the secondary amine.

The Reaction of α-Cyanolycopodine with Benzaldehyde

One gram of α-cyanolycopodine and 0.74 gm. of benzaldehyde were dissoved in absolute methanol in a flask equipped with a dropping funnel and reflux condenser. A solution of sodium methoxide in absolute methanol (4 cc. of a solution prepared from 12 gm. of sodium in 150 cc. of methanol) was added to the refluxing solution over a period of 15 min. The reaction mixture was allowed to stand overnight at room temperature and after it had been left for several hours in the refrigerator, crystallization occurred. The first crop of crystals (0.40 gm.) was recrystallized from methanol, to give glistening yellow crystals, m.p. 179.5–180.5°.

The filtrate was concentrated on the steam cone and the residue poured into water to yield an amorphous mass which immediately solidified on warming on the steam cone. The precipitate was collected and dried to yield an additional 0.83 gm. of crude benzylidene derivative. Total yield = 93%.

Calc. for $C_{24}H_{30}ON_2$: C, 79.50; H, 8.35; N, 7.74.
Found: C, 79.52, 79.36; H, 8.34, 8.19; N, 7.80, 7.85.

The infrared spectrum in carbon disulphide contained aromatic absorption bands at 3050 cm.$^{-1}$, 3017 cm.$^{-1}$, and 1617 cm.$^{-1}$; carbonyl absorption at 1690 cm.$^{-1}$; and nitrile absorption at 2215 cm.$^{-1}$. In nujol there was aromatic absorption at 1607 cm.$^{-1}$, carbonyl absorption at 1681 cm.$^{-1}$, and nitrile absorption at 2205 cm.$^{-1}$.

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THE STRUCTURE OF HYOCHOLIC ACID[1]

By P. Ziegler

ABSTRACT

Further evidence for the α-configuration of the hydroxyl groups in hyocholic acid is presented and several related compounds are described.

Two reports (2, 4) have appeared recently describing the isolation and chemistry of hyocholic acid. This compound, derived from hog bile, was characterized as 3α,6α,7α-trihydroxycholanic acid. In order to determine the stereochemical configuration of the hydroxyl groups in ring B, Haslewood (2) partially acetylated ethyl hyocholate to the corresponding 3,6-diacetate (II*b*). Oxidation of II*b* followed by hot alkaline hydrolysis provided a compound of m.p. 211–215°C. and $[\alpha]_D^{23}$ +12.3° (ethanol) to which structure IV was arbitrarily assigned. This finding does not agree with the results of Takeda *et al.* (3) who claimed to have isolated IV, m.p. 183–185°C. and $[\alpha]_D^{15}$ −62.5° (methanol), by very mild saponification of 3α-acetoxy-6α-bromo-7-ketocholanic acid methyl ester. The Japanese authors mentioned that their compound IV yielded the well-known 3α,6α-dihydroxycholanic acid (hyodesoxycholic acid) on reaction with ethanedithiol and subsequent reduction with Raney nickel; however, no experimental evidence for this transformation was cited. They also showed that IV, on being refluxed with methanolic potassium hydroxide, readily isomerized to a product of m.p. 227°C. and $[\alpha]_D^{15}$ +46.4° (methanol) which they characterized as 3α,7-dihydroxy-6-keto-allocholanic acid. Furthermore, this latter compound was the sole material isolated after hot alkaline hydrolysis of the 6-bromo-steroid mentioned before.

Our evidence (4) for the α-configuration of the hydroxyl groups in ring B of hyocholic acid was based on acetonide formation and on optical rotation data. To obtain more rigorous proof, a reaction scheme very similar to that of Haslewood (2) was investigated. We acetylated methyl hyocholate and isolated a crystalline fraction which unfortunately could not be purified chromatographically to a constant melting point. It was therefore decided to forego isolation at this stage, and the entire reaction mixture (crude II*a*) was subsequently oxidized with chromic acid; no crystalline product was obtained. It may be mentioned that Takeda *et al.* (3) also were unable to isolate III in crystalline form. Part of crude III was then saponified under very mild conditions to provide IV, m.p. 180–183°C. and $[\alpha]_D^{25}$ −47.5° (methanol). More drastic alkaline hydrolysis yielded a different product (V), m.p. 234–236°C. and $[\alpha]_D^{25}$ +39.6° (methanol). Both these findings are in accord with the results of the Japanese authors (3). The product isolated by Haslewood (2) and assigned structure IV is probably a mixture of the two isomers IV and V. This can readily be explained by analogy to the ketol rearrangements observed

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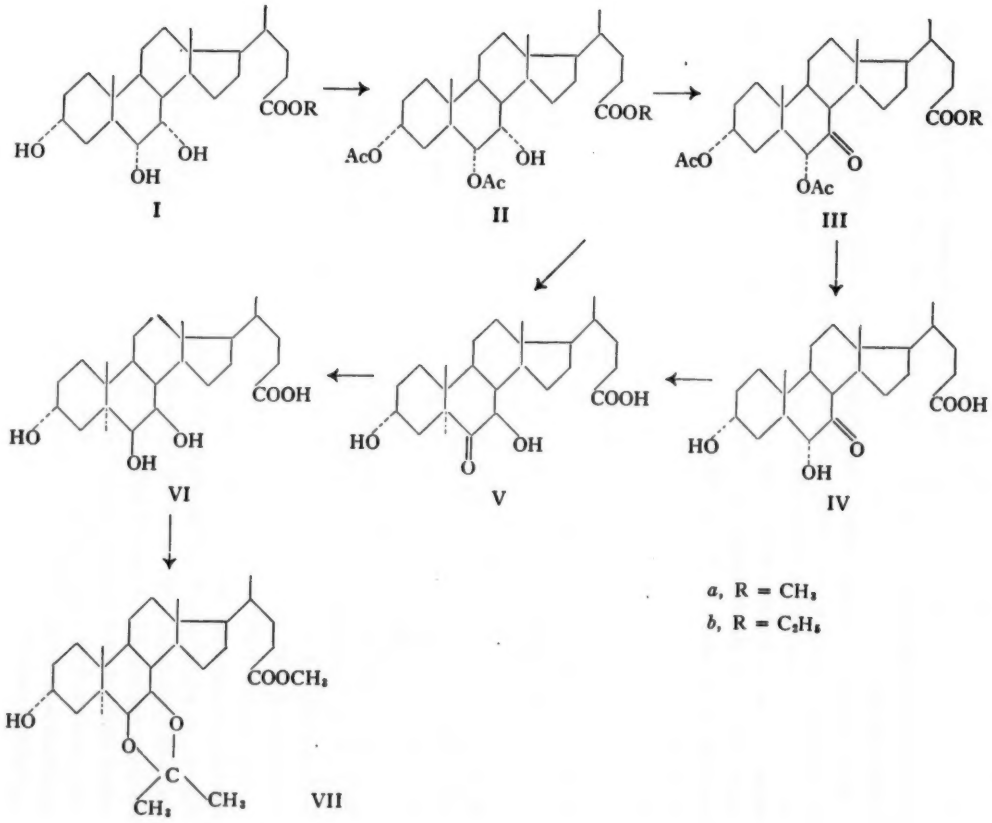

a, R = CH_3
b, R = C_2H_5

in ring C of the steroids. Borgstrom and Gallagher (1) found that 3α,12β-dihydroxy-11-ketocholanic acid, on being refluxed with hot alkali, yielded a mixture from which all four possible isomers were isolated. As expected the two isomers having the hydroxyl group in the more stable equatorial conformation predominated and accounted for 94% of the products. In compound IV, the 6α-hydroxyl group is also equatorial but in contact with hot alkali isomerizes to the intermediate 3α,7β-dihydroxy-6-ketocholanic acid. This compound, in turn, readily isomerizes to the thermodynamically more stable product V in which the ring A/B junction is *trans* and the 7β-hydroxyl group is equatorial.

Reduction of V with sodium borohydride expectedly yielded VI, having the 6β-hydroxyl function in the axial conformation. This compound gave a well-defined, crystalline acetonide on treatment with acetone and *p*-toluenesulphonic acid, which showed that both hydroxyl groups in ring B of VI must have the β-configuration. These data therefore clearly establish the structures of V and VI. The fact that III gave rise to the two isomers, IV or V, depending on the conditions of alkaline hydrolysis, lends further support to the previously assigned stereochemistry of hyocholic acid.

EXPERIMENTAL[2]

3α,6α-Diacetoxy-7-ketocholanic Acid Methyl Ester (IIIa)

Methyl hyocholate (I*a*; 2.75 gm.) was acetylated at 20°C. with pyridine (12 ml.) and acetic anhydride (20 ml.). After 20 hr., the solvents were removed *in vacuo* at 30°C. and the residue was taken up in ether and dilute mineral acid. The solvent extract was washed, dried, and evaporated to provide a gum (3.4 gm.) which crystallized from hexane–ether, giving 770 mgm. of material, m.p. 130°C. This fraction, on recrystallization from the same solvents, gave m.p. 140–155°C. and chromatography on alumina (acid washed) gave crystalline fractions, none of which exhibited sharp melting points. Since isolation of II*a* in pure form could not be achieved, the solid product was recombined with the remaining gum.

The entire residue from the acetylation (crude II*a*; 3.4 gm.) was then dissolved in acetic acid (25 ml.) and water (5 ml.), and the solution was cooled in an ice bath. After dropwise addition of a solution of chromium trioxide (0.5 gm.) in 80% acetic acid (10 ml.), the mixture was kept at 0°C. for two hours. The reaction products were diluted with water containing a small amount of sulphuric acid, extracted with ether, and the solvent extract was washed with dilute sulphuric acid, then with water. Drying over sodium sulphate and evaporation of the ether provided a residue (III*a*; 3.4 gm.)which failed to crystallize.

3α,6α-Dihydroxy-7-ketocholanic Acid (IV)

Crude III*a* (400 mgm.) was dissolved in methanol (10 ml.) and there was then added a solution of potassium hydroxide (150 mgm.) in water (2 ml.). After 40 hr. at 20°C., the pale yellow solution was poured into dilute hydrochloric acid and the mixture was extracted with ether. The extract was washed

[2]*The microanalyses were kindly performed by Mr. E. Thommen, Basel, Switzerland.*

with water, dried, and evaporated. The residue was dissolved in a small volume of ether and refrigerated to yield 50 mgm. of material, m.p. 177–178°C. Recrystallization from ethyl acetate gave IV, m.p. 180–183°C. and $[\alpha]_D^{25}$ −47.5° (*c*, 0.393, methanol). Analysis: Calc. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42; O, 19.68. Found: C, 71.20; H, 9.52; O, 19.39. This compound did not give a coloration with alcoholic ferric chloride solution.

3α,7β-Dihydroxy-6-keto-allocholanic Acid (*V*)

Crude III*a* (270 mgm.) was refluxed for one and a half hours with 4% methanolic potassium hydroxide (10 ml.). Most of the solvent was evaporated *in vacuo*, the residue was acidified and extracted with ether. The solvent extract was washed with water, dried over sodium sulphate, filtered, and evaporated to dryness. The residue crystallized from ether to provide 60 mgm. of material, m.p. 213–215°C. Two recrystallizations from methanol gave pure V, m.p. 234–236°C. and $[\alpha]_D^{25}$ +39.6° (*c*, 0.19, methanol). Analysis: Calc. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42; O, 19.68. Found: C, 71.08, 70.94; H, 9.43, 9.58; O, 19.65, 19.76.

3α,6β,7β-Trihydroxy-allocholanic Acid (*VI*)

Compound V (505 mgm.) was suspended in methanol (25 ml.) and there was then added, during a period of three hours, 1.5 gm. of sodium borohydride. The solution was diluted with water, acidified, and the resulting precipitate was filtered off. The solid was dissolved in a mixture of ethyl acetate and methanol, the solution was distilled to remove the methanol, and, on cooling, crystals formed. These were filtered to give 453 mgm. of material, m.p. 253–255°C.; one further recrystallization yielded pure VI, m.p. 256–257°C. and $[\alpha]_D^{25}$ +49.5° (*c*, 0.417, ethanol). Analysis: Calc. for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87; O, 19.58. Found: C, 70.74, 70.58; H, 9.73, 9.97; O, 20.00

The methyl ester of VI, prepared by reaction with ethereal diazomethane, was crystallized from ether–hexane to give m.p. 142–144°C. and $[\alpha]_D^{23}$ +47.9° (*c*, 0.624, ethanol).

Acetonide VII

Compound VI (150 mgm.), after methylation with diazomethane, was dissolved in dry acetone (10 ml.). After addition of *p*-toluenesulphonic acid (30 mgm.), the solution was kept at 20°C. for 15 hr. The acid was then neutralized with sodium bicarbonate, the mixture was poured into water, and the products were extracted with ether. The solvent extract was worked up in the usual manner to yield a residue which crystallized from a mixture of ether and iso-octane. The crystals (139 mgm.), m.p. 115–119°C., were recrystallized from the same solvents to give thin needles of VII, m.p. 118–120°C. and $[\alpha]_D^{25}$ +57.4° (*c*, 0.62, ethanol). Analysis: Calc. for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02; O, 17.29. Found: C, 72.77, 72.51; H, 10.08, 9.94; O, 16.74.

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TOXIC FLUORINE COMPOUNDS

XII. ESTERS OF ω-FLUOROALCOHOLS[1]

By J. E. Millington and F. L. M. Pattison

ABSTRACT

Representative members of the series of ω-fluoroalkyl methanesulphonates, *p*-toluenesulphonates, acetates, and benzoates have been prepared, and some of their chemical, physical, and toxicological properties determined.

The four classes of esters described in this paper were prepared for toxicological studies; by comparison with the results previously reported for the parent ω-fluoroalcohols (22), it was hoped that information could be obtained regarding the hydrolysis *in vivo* of the different ester groupings. The ω-fluoroalkyl sulphonates were also required as intermediates in the synthesis of other ω-fluorinated compounds, notably iodides (21), thiocyanates (15), thiolacetates (15), and sulphonyl chlorides (18), while the ω-fluoroalkyl acetates and benzoates afforded a convenient means of preparing some of the less stable ω-fluoroalcohols, such as 4-fluorobutanol and 5-fluoropentanol.

PREPARATION

The ω-fluoroalkyl methanesulphonates and *p*-toluenesulphonates were prepared either by esterification of the requisite ω-fluoroalcohols (22) with methanesulphonyl or *p*-toluenesulphonyl chloride, or by the metathesis of ω-fluoroalkyl halides (14, 21) with silver methanesulphonate or *p*-toluenesulphonate (7). Yields are summarized in Tables I and II.

ω-Fluoroalkyl acetates were prepared by fluorination of ω-chloroalkyl acetates, which in turn were prepared either by acetylation of the corresponding ω-chloroalcohols or by ring cleavage of cyclic ethers using acetyl chloride (1, 4, 27). Fluorination with potassium fluoride under pressure in an autoclave as originally recommended by Gryszkiewicz-Trochimowski, Sporzynski, and Wnuk (10) was found to be satisfactory, although disproportionation to polymethylene diacetates and formation of unsaturated compounds by loss of hydrogen halides lowered the yields of the ω-fluoroalkyl acetates. Fluorination of 4-chlorobutyl and 5-chloroamyl acetates with potassium fluoride in diethylene glycol resulted in extensive formation of tetrahydrofuran and tetrahydropyran, due to hydrolysis and hydrogen halide elimination in the alkaline medium, with only small amounts of the ω-fluoroalkyl acetates being obtained. Results of these reactions are summarized in Tables III and IV.

The ω-fluoroalkyl acetates were converted to the parent ω-fluoroalcohols by transesterification or by previously described methods (22) (Table V). Because of the relatively poor yields in the fluorination of the ω-chloroalkyl acetates,

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For Part XI, see Ref. 30.

TABLE I

PREPARATION AND PHYSICAL CONSTANTS OF ω-FLUOROALKYL METHANESULPHONATES

Methanesulphonate	Method of preparation[a]	Yield, %	Boiling point		n_D^{25}
			°C.	mm.	
2-Fluoroethyl methanesulphonate	I	31	118–119	12	1.4145
3-Fluoropropyl methanesulphonate	I	37	84	2	1.4183
4-Fluorobutyl methanesulphonate	II[b]	82	89–90	0.5	1.4242
5-Fluoroamyl methanesulphonate	II[c]	90	112	2	1.4290
6-Fluorohexyl methanesulphonate	I	69	130–131	2.5	1.4315

[a] *Method of preparation: I: esterification of ω-fluoroalcohol with methanesulphonyl chloride in the presence of pyridine; II: metathesis of ω-fluoroalkyl halide with silver methanesulphonate.*
[b] *From 4-fluorobutyl iodide.*
[c] *From 5-fluoroamyl bromide.*

TABLE II

PREPARATION AND PHYSICAL CONSTANTS OF ω-FLUOROALKYL *p*-TOLUENESULPHONATES

p-Toluenesulphonate	Method of preparation[a]	Yield, %	Boiling point		n_D^{25}
			°C.	mm.	
2-Fluoroethyl *p*-toluenesulphonate[b,c]	I	80	138.5–140	1	1.5060
3-Fluoropropyl *p*-toluenesulphonate	I	78	160	2	1.5013
4-Fluorobutyl *p*-toluenesulphonate[c]	II	91	151	1	1.4988
5-Fluoroamyl *p*-toluenesulphonate	I	54	163	0.6	1.4970

[a] *Method of preparation: I: esterification of ω-fluoroalcohol with p-toluenesulphonyl chloride in the presence of pyridine; II: metathesis of 4-fluorobutyl iodide with silver p-toluenesulphonate.*
[b] *Childs et al. (3) report b.p. 135–136° at 1 mm.*
[c] *Preparative details have been reported previously (15).*

TABLE III

PREPARATION AND PHYSICAL CONSTANTS OF ω-CHLOROALKYL ACETATES

Acetate	Method of preparation[a]	Yield, %	Boiling point		n_D^{25}
			°C.	mm.	
2-Chloroethyl acetate[b]	I	84.5	140–144	750	1.4220
3-Chloropropyl acetate[c]	I	81.5	61–64	10	1.4273
4-Chlorobutyl acetate[d]	II	80	84–88	15	1.4320
5-Chloroamyl acetate[e]	II	95	96–98	11	1.4363

[a] *Method of preparation: I: acetylation of ω-chloroalcohol; II: cleavage of cyclic ether with acetyl chloride.*
[b] *Suter and Evans (26) report b.p. 145°.*
[c] *Lespieau (17) reports b.p. 62.3° at 10 mm. and* n_D^{21} *1.431.*
[d] *Bennett and Heathcoat (2) report b.p. 87° at 17 mm.*
[e] *Synerholm (27) reports b.p. 104° at 18 mm.*

the over-all yields to ω-fluoroalcohols were unsatisfactory. Accordingly, fluorination of ω-chloroalkyl benzoates was next examined; it was hoped that by thus altering the acid moiety and hence its influence on the reaction, the yields in the replacement of chlorine by fluorine would be increased.

TABLE IV

PREPARATION AND PHYSICAL CONSTANTS OF ω-FLUOROALKYL ACETATES

Acetate	Method of preparation[a]	Temp., °C.	Time, hr.	Yield, %	Boiling point °C.	Boiling point mm.	n_D^{25}
2-Fluoroethyl acetate[b]	I	150	48	20	115–119	750	
	I	200	48	41.5	116–117.5	740	1.3784
3-Fluoropropyl acetate[c]	I	200	49	38	41–44	11	1.3863
4-Fluorobutyl acetate[d]	I	240	48	66	56–57	12	1.3949
	II	90	16	12.6	66–68	20	
5-Fluoroamyl acetate[e]	I	200	48	6	72–76	14	
	I	250	120	32	70–71	12	1.4017
	II	93	9	29	71–72	12	
By-products isolated from autoclave fluorinations (Method I)							
Ethylene diacetate[f]					79–81	12	1.4175
Trimethylene diacetate[g]					95	13	1.4206
Pentamethylene diacetate[h]					122	12	1.4262
Pent-4-en-1-yl acetate[i]					46–47	12	1.4159

[a] *Method of preparation: I: autoclave fluorination with potassium fluoride and no solvent; II: fluorination at atmospheric pressure with potassium fluoride in ethylene or diethylene glycol.*

[b] *Knunyants et al. (16) report b.p. 115–116° and* n_D^{20} *1.3820.*

[c] *Gryszkiewicz-Trochimowski et al. (10) report b.p. 137–138°.*

[d] *Gryszkiewicz-Trochimowski et al. (10) report b.p. 55.5–56.0° at 11 mm.*

[e] *Pattison et al. (22) report b.p. 71–72.5° at 11 mm.*

[f] *Wurtz (31) reports b.p. 186–187°.*

[g] *Reboul (24) reports b.p. 209–210°.*

[h] *Hamonet (11) reports b.p. 241°.*

[i] *Paul (23) reports b.p. 150–151° and* n_D^{19} *1.4176.*

TABLE V

PREPARATION AND PHYSICAL CONSTANTS OF ω-FLUOROALCOHOLS

Alcohol	Method of preparation[a]	Yield, %	Boiling point °C.	Boiling point mm.	n_D^{25}
3-Fluoropropanol[b]	I	64	34	11	1.3801
4-Fluorobutanol[c]	II	86	52–55	9	1.3945
	III	54.5	63–65	18	1.3948
5-Fluoropentanol[d]	II	87	71–72	12	
	III	76	71–72	11	
	IV	90	66–67	10	1.4050

[a] *Method of preparation: I: transesterification of ω-fluoroalkyl benzoate; II: acid hydrolysis (9, 22) of ω-fluoroalkyl acetate; III: reductive debenzoylation of ω-fluoroalkyl benzoate; IV: transesterification of ω-fluoroalkyl acetate.*

[b] *Hoffmann (14) reports b.p. 127.8° and* n_D^{25} *1.3771.*

[c] *Gryszkiewicz-Trochimowski (9) reports b.p. 52–53° at 11 mm.*

[d] *Pattison et al. (22) report b.p. 70–71° at 11 mm. and* n_D^{25} *1.4057.*

The ω-chloroalkyl benzoates were prepared either by benzoylation of ω-chloroalcohols or by ring cleavage of the appropriate cyclic ethers using benzoyl chloride (27, 28). Fluorination in the autoclave still resulted in disproportionation to polymethylene dibenzoates, but the yields of ω-fluoroalkyl benzoates were good, showing considerable improvement over those of the corresponding ω-fluoroalkyl acetates. Fluorination of 4-chlorobutyl and 5-chloroamyl benzo-

ates in diethylene glycol proceeded in very low yield; thus, in the fluorination of 4-chlorobutyl benzoate, isolated by-products included tetrahydrofuran, formed by ring closure, and the mono- and *bis*-(4-benzoyloxybutyl) ethers of diethylene glycol ($HO(CH_2)_2O(CH_2)_2O(CH_2)_4OCOC_6H_5$ and $C_6H_5COO(CH_2)_4O(CH_2)_2O(CH_2)_2O(CH_2)_4OCOC_6H_5$), formed by reaction with the solvent. Results of these reactions are summarized in Tables VI and VII.

TABLE VI

PREPARATION AND PHYSICAL CONSTANTS OF ω-CHLOROALKYL BENZOATES

Benzoate	Method of preparation[a]	Yield, %	Boiling point		n_D^{25}
			°C.	mm.	
2-Chloroethyl benzoate[b]	I	91	118–119	3	1.5249
	II[c]	35	112	1	
3-Chloropropyl benzoate[d]	I	79	130–131	2.5	1.5222
4-Chlorobutyl benzoate[e]	II	89	142	2	1.5180
5-Chloroamyl benzoate[f]	II	74	127–130	0.9	1.5140

[a] *Method of preparation: I: benzoylation of ω-chloroalcohol; II: cleavage of cyclic ether with benzoyl chloride.*

[b] *Dobryanskii and Sivertsev (6) report b.p. 139–140° at 40 mm. and* n_D^{20} *1.5283.*

[c] *2-Chloroethoxyethyl benzoate,* $ClCH_2CH_2OCH_2CH_2OCOC_6H_5$, *was also isolated in 34% yield, b.p. 130–132° at 1 mm. and* n_D^{25} *1.5186; Cretcher and Pittenger (5) report b.p. 191° at 25 mm.*

[d] *Zaki (32) reports b.p. 155–156° at 15 mm.*

[e] *Synerholm (28) reports b.p. 132–135° at 2.5 mm. and* n_D^{25} *1.5176.*

[f] *Synerholm (27) reports b.p. 141–143° at 2 mm. and* n_D^{20} *1.5169.*

TABLE VII

PREPARATION AND PHYSICAL CONSTANTS OF ω-FLUOROALKYL BENZOATES

Benzoate	Method of preparation[a]	Temp., °C.	Time, hr.	Yield, %	Boiling point		M.p. or n_D^{25}
					°C.	mm.	
2-Fluoroethyl benzoate[b]	I	225	48	79	112–114	10	1.5001
3-Fluoropropyl benzoate	I	210	48	77	126–127	10	1.4962
4-Fluorobutyl benzoate	I	220	48	76	142–143	10	1.4940
	II	120	13	14	121	2	1.4932
5-Fluoroamyl benzoate	I	220	48	57	122	1.5	
	II	115	15	19	156–157	11	1.4912
By-products isolated from autoclave fluorinations (Method I)							
Ethylene dibenzoate[c]							70.5–71
Trimethylene dibenzoate[d]							56–57
Tetramethylene dibenzoate[e]							80
Pentamethylene dibenzoate					174	0.001	1.5397
By-products isolated from diethylene glycol fluorinations (Method II)							
Diethylene glycol mono-(4-benzoyloxybutyl) ether					155	2	1.5179
Diethylene glycol *bis*-(4-benzoyloxybutyl) ether					176	0.2	1.5378

[a] *Method of preparation: I: autoclave fluorination with potassium fluoride and no solvent; II: fluorination at atmospheric pressure with potassium fluoride in diethylene glycol.*

[b] *Schrader (25) reports b.p. 105–107° at 12 mm.; Pattison et al. (20) report b.p. 106–108° at 10 mm. and* n_D^{25} *1.4998.*

[c] *Varvoglis (29) reports m.p. 72–73°.*

[d] *Heim and Poe (12) report m.p. 53°.*

[e] *Gol'dfarb and Smorgonskii (8) report m.p. 80–81°.*

The ω-fluoroalkyl benzoates were converted to ω-fluoroalcohols either by transesterification or by reductive debenzoylation with lithium aluminum hydride. Results are listed in Table V.

From a consideration of this and earlier studies, the following are the recommended procedures for the preparation of the lower ω-fluoroalcohols: 2-fluoroethanol: direct fluorination of 2-chloroethanol (13); 3-fluoropropanol: direct fluorination of 3-chloropropanol (14, 22); 4-fluorobutanol: autoclave fluorination of 4-chlorobutyl acetate followed by acid hydrolysis; 5-fluoropentanol: autoclave fluorination of 5-chloroamyl benzoate followed by reductive debenzoylation. Optimum conditions for the preparation of the higher ω-fluoroalcohols have been described previously (22).

TOXICITY

The toxicities of the ω-fluoroalkyl esters are shown in Table VIII. The most striking feature is the relative lack of toxicity of 2-fluoroethyl methanesulphonate and *p*-toluenesulphonate. Since 2-fluoroethanol has a toxicity of 10 mgm./kgm., the conclusion may be drawn that these sulphonate esters are not readily hydrolyzed *in vivo*. On the other hand, the fact that the higher members follow the usual dichotomous pattern suggests (19) that hydrolysis is occurring, giving rise to the parent ω-fluoroalcohols.

The ω-fluoroalkyl acetates and benzoates conform very closely to the pattern previously described for the ω-fluoroalcohols; moreover, on a molar basis, the LD_{50} figures for these esters are very similar to those for the parent ω-fluoroalcohols, indicating that they are hydrolyzed readily *in vivo*.

TABLE VIII

TOXICITY OF ω-FLUOROALKYL ESTERS

Value of n in $F(CH_2)_nOX$	LD_{50} for mice (intraperitoneal), mgm./kgm.			
	X = SO_2CH_3	X = $SO_2C_6H_4CH_3$	X = $COCH_3$	X = COC_6H_5
2	*ca.* 100	>100	18.6	38
3	>100	>100	77.6	>100
4	1.0	30	0.96	1.7
5	>100	>100	>100	>100
6	35	—	—	—

It has become increasingly apparent in our study of the toxic effects of the ω-fluorine atom that the 2-fluoroethyl compound in any series is considerably less toxic than the higher even members in the same series. This is borne out in the case of ω-fluorinated alcohols, halides, nitriles, thiocyanates, thiolacetates, acids, aldehydes, etc., all of which have been described earlier. The four classes of esters described herein are consistent with this observation, as can be seen from Table VIII. No work has yet been carried out to determine the cause of this anomaly, but it seems reasonable to surmise that the intramolecular electronic influence of the 2-fluorine atom on the other functional groups (with resultant interference with metabolic breakdown) probably outweighs solubility and steric effects.

TABLE IX

ANALYTICAL DATA FOR NEW COMPOUNDS

Compound	C, %		H, %		S, %	
	Calc.	Found	Calc.	Found	Calc.	Found
$F(CH_2)_2OSO_2CH_3$	25.35	25.48	4.93	4.99		
$F(CH_2)_3OSO_2CH_3$	30.76	30.71	5.76	5.73		
$F(CH_2)_4OSO_2CH_3$	35.28	35.52	6.51	6.81	18.84	18.50
$F(CH_2)_5OSO_2CH_3$	39.11	39.25	7.11	7.03	17.41	17.29
$F(CH_2)_6OSO_2CH_3$	42.41	42.32	7.62	7.46	16.17	16.03
$F(CH_2)_3OSO_2C_6H_4CH_3$	51.71	51.93	5.64	5.48		
$F(CH_2)_5OSO_2C_6H_4CH_3$	55.36	55.48	6.58	6.44		
$F(CH_2)_3OCOC_6H_5$	65.97	66.10	6.08	6.00		
$F(CH_2)_4OCOC_6H_5$	67.35	67.40	6.63	6.63		
$F(CH_2)_5OCOC_6H_5$	68.60	68.45	7.14	7.44		
$C_6H_5COO(CH_2)_6OCOC_6H_5$	73.05	73.29	6.45	6.39		
$HO(CH_2)_2O(CH_2)_2O(CH_2)_4OCOC_6H_5$	63.83	63.66	7.80	7.72		
$[C_6H_5COO(CH_2)_4O(CH_2)_2]_2O$	68.10	68.32	7.47	7.35		

EXPERIMENTAL[2,3]

Preparation of ω-Fluoroalkyl Methanesulphonates and p-Toluenesulphonates

The following syntheses are representative of the methods employed for the preparation of ω-fluoroalkyl methanesulphonates and *p*-toluenesulphonates.

Method I: the Reaction of a Fluoroalcohol with a Sulphonyl Chloride

3-Fluoropropyl p-toluenesulphonate.—A mixture of *p*-toluenesulphonyl chloride (30.5 gm., 0.16 mole) and pyridine (40 gm.) was stirred at −2°, and 3-fluoropropanol (14) (12.5 gm., 0.16 mole) was added dropwise over two hours. Stirring was continued for a further two hours. The reaction mixture was diluted with water and 6 *N* hydrochloric acid until there was no pyridine odor, and then extracted with ether. The combined extracts were washed successively with water, aqueous sodium carbonate, and water again, and dried over anhydrous sodium sulphate. After removal of the ether, fractionation of the residue yielded 29 gm. (78%) of 3-fluoropropyl *p*-toluenesulphonate.

Method II: the Reaction of a Fluoroalkyl Halide with the Silver Salt of a Sulphonic Acid

5-Fluoroamyl methanesulphonate.—A mixture of 5-fluoroamyl bromide (21) (12.0 gm., 0.07 mole), silver methanesulphonate (14.3 gm., 0.07 mole), and acetonitrile (50 ml.) was heated on a steam bath for one hour. Silver bromide was removed from the cooled mixture by filtration, and the acetonitrile was distilled Fractionation of the residue yielded 5-fluoroamyl methanesulphonate (11.7 gm., 90%).

Preparation of ω-Chloroalkyl Acetates

The following are representative examples of the procedures employed in the preparation of ω-chloroalkyl acetates.

[2]*Analysis results are shown in Table IX.*

[3]*Physical constants are shown in the appropriate tables. Several of the compounds have been described in the literature; their constants are listed herein as criteria of purity and to provide some previously unreported refractive indices.*

Method I: the Reaction of an Alcohol with Acetyl Chloride

3-Chloropropyl acetate.—A mixture of 3-chloropropanol (118.2 gm., 1.25 moles) and acetyl chloride (100 gm., 1.27 moles) was heated on a water bath (60°) for one hour. It was cooled, washed successively with water and aqueous sodium carbonate, and transferred to a flask fitted for distillation. Ethylene chloride (50 ml.) was added and the water – ethylene chloride azeotrope distilled. The residue on fractionation through a 50 cm. Vigreux column gave 3-chloropropyl acetate (139 gm., 81.5%).

Method II: the Reaction of a Cyclic Ether with Acetyl Chloride

5-Chloroamyl acetate.—Acetyl chloride (110 gm., 1.40 moles) was added with constant stirring to an ice-cooled mixture of redistilled tetrahydropyran (107.5 gm., 1.25 moles) and freshly fused and ground zinc chloride (2.7 gm.). When the addition was complete, the mixture was heated on a steam bath for five hours and then fractionated to give 5-chloroamyl acetate (195 gm., 95%).

Preparation of ω-Fluoroalkyl Acetates

The ω-fluoroalkyl acetates were prepared by one or both of the procedures outlined below.

Method I: Autoclave Method, No Solvent

5-Fluoroamyl acetate.—A mixture of 5-chloroamyl acetate (335 gm., 2.02 moles) and anhydrous potassium fluoride (232 gm., 4.0 moles) was heated in a stainless steel autoclave at 250° for 120 hr. After the autoclave had cooled, the mixture was diluted with water and the layers were separated. The aqueous layer was extracted with ether. The organic layer and extracts were combined, washed with water and aqueous sodium carbonate, and then dried. The ether was distilled, and the residue on fractionation through a modified Podbielniak column gave pent-4-en-1-yl acetate (27.2 gm.), 5-fluoroamyl acetate (95.6 gm., 32%), and pentamethylene diacetate (47.7 gm.).

Method II: Atmospheric Pressure, Diethylene Glycol as Solvent

5-Fluoroamyl acetate.—A mixture of 5-chloroamyl acetate (46 gm., 0.28 mole), anhydrous potassium fluoride (48 gm., 0.83 mole), and diethylene glycol (250 gm.) was heated with constant stirring at 93° for nine hours. Earlier experiments had shown that higher temperatures resulted in lower yields of fluoro ester, and that the use of potassium iodide as a promoter did not increase the yield. The mixture was distilled through a 20 cm. Vigreux column first at atmospheric pressure, giving tetrahydropyran (4.6 gm.), and then under reduced pressure up to the boiling point of diethylene glycol. This material was dissolved in ether, dried over anhydrous sodium sulphate, and fractionated through a 30 cm. Vigreux column, giving 5-fluoroamyl acetate (12 gm., 29%).

Preparation of ω-Chloroalkyl Benzoates

The ω-chloroalkyl benzoates were prepared by procedures analogous to those employed for the ω-chloroalkyl acetates.

Method I: the Reaction of an Alcohol with Benzoyl Chloride

3-Chloropropyl benzoate.—3-Chloropropanol (100 gm., 1.06 moles) was added with constant stirring to an ice-cooled mixture of benzoyl chloride (150 gm., 1.06 moles), pyridine (85 gm., 1.07 moles), and anhydrous ether (100 ml.). When the addition was complete, the mixture was stirred at room temperature for 2.5 hr., diluted with water, and extracted with ether. The combined extracts were washed successively with water, aqueous sodium carbonate, and water again, and dried over anhydrous calcium chloride. The ether was removed on the water bath and the residue on fractionation through a 25 cm. Vigreux column gave 3-chloropropyl benzoate (164.6 gm., 79%).

Method II: the Reaction of a Cyclic Ether with Benzoyl Chloride

2-Chloroethyl benzoate.—Benzoyl chloride (70.25 gm., 0.5 mole) was added over 1.8 hr. to a well-stirred mixture of ethylene oxide (44 gm., 1.0 mole) and freshly fused zinc chloride (3 gm.), cooled in an ice–salt bath. The mixture was stirred for a further two hours, and then heated on a steam bath for 30 min. The mixture was cooled, diluted with water, and extracted with ether. The extracts were washed with water and dried over anhydrous calcium chloride. The ether was distilled and fractionation of the residue gave 2-chloroethyl benzoate (32.5 gm., 35%), 2-chloroethoxyethyl benzoate (39.1 gm., 34%), and ethylene dibenzoate (16 gm.).

Preparation of ω-Fluoroalkyl Benzoates

Below are outlined the procedures which were employed for the preparation of ω-fluoroalkyl benzoates.

Method I: Autoclave Method, No Solvent

2-Fluoroethyl benzoate.—A mixture of 2-chloroethyl benzoate (167 gm., 0.91 mole) and anhydrous potassium fluoride (116 gm., 2.0 moles) was heated in a stainless steel autoclave with mechanical stirring at 225° for 48 hr. After the autoclave had cooled, the mixture was diluted with water and extracted with ether. The combined extracts were washed with water and dried over anhydrous calcium chloride. Removal of the ether and fractionation of the product gave 2-fluoroethyl benzoate (86 gm.), unchanged 2-chloroethyl benzoate (48 gm.), and ethylene dibenzoate (4 gm.). This represents a yield of 79% based on reacted starting material.

Method II: Atmospheric Pressure, Diethylene Glycol as Solvent

4-Fluorobutyl benzoate.—A mixture of 4-chlorobutyl benzoate (106.3 gm., 0.5 mole), anhydrous potassium fluoride (116 gm., 2.0 moles), and diethylene glycol (200 gm.) was heated at 120° with constant stirring for 13 hr. The mixture was cooled, diluted with water, and extracted with ether. The extracts were washed with water and dried over anhydrous magnesium sulphate. The ether was distilled and the residue fractionated to give a small forerun of 4-fluorobutanol, and then 4-fluorobutyl benzoate (12 gm., 14%), 4-chlorobutyl benzoate (16.5 gm.), diethylene glycol mono-(4-benzoyloxybutyl) ether (40.5 gm.), and diethylene glycol *bis*-(4-benzoyloxybutyl) ether (6 gm.).

Preparation of ω-Fluoroalcohols

The ω-fluoroalcohols were prepared by the procedures outlined below.

Method I: Transesterification of ω-Fluoroalkyl Benzoate

3-Fluoropropanol.—A mixture of 3-fluoropropyl benzoate (18.2 gm., 0.1 mole), *p*-toluenesulphonic acid (0.5 gm.), and absolute methanol (100 ml.) was heated under reflux for 12 hr. Fractionation of the product gave 3-fluoropropanol (5.0 gm., 64%).

Method II: Acid Hydrolysis of ω-Fluoroalkyl Acetate

4-Fluorobutanol.—A mixture of 4-fluorobutyl acetate (172 gm., 1.28 moles) and 5% aqueous sulphuric acid (600 ml.) was heated under reflux until homogeneous (*ca.* 30 min.). The mixture was cooled, saturated with solid sodium bicarbonate, and extracted with ether. The extracts were dried over anhydrous sodium sulphate, the ether was removed, and the residue was fractionated to give 4-fluorobutanol (101 gm., 86%).

Method III: Reductive Debenzoylation of ω-Fluoroalkyl Benzoate

5-Fluoropentanol.—A solution of 5-fluoroamyl benzoate (13.3 gm., 0.064 mole) in anhydrous ether (125 ml.) was added with constant stirring to a suspension of lithium aluminum hydride (3.2 gm., 0.083 mole) in anhydrous ether (200 ml.) at such a rate that the ether boiled gently under reflux. When the addition was complete, the mixture was stirred for a further 30 min. Water was added to decompose the excess hydride, the reaction flask being cooled in an ice bath. The complex was hydrolyzed with 10% aqueous sulphuric acid and the ethereal layer was separated. The aqueous layer was extracted with ether and the combined extracts were dried over anhydrous potassium carbonate. The ether was removed on the water bath and the residue on fractionation gave 5-fluoropentanol (5.1 gm., 76%).

Method IV: Transesterification of ω-Fluoroalkyl Acetate

5-Fluoropentanol.—A mixture of 5-fluoroamyl acetate (44.4 gm., 0.30 mole), *p*-toluenesulphonic acid (0.5 gm.), and absolute methanol (150 ml.) was heated under reflux for 19.5 hr. Fractionation of the product gave 5-fluoropentanol (28.5 gm., 90%).

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LIGHT ABSORPTION STUDIES

PART VI. THE EFFECTIVE INTERFERENCE VALUES OF NON-BONDED ATOMS IN SOLUTION. PART I. SOME PRELIMINARY OBSERVATIONS[1]

By W. F. Forbes and W. A. Mueller

ABSTRACT

The application of light absorption data to determine minimum interference radii of various atoms in solution is examined. Three separate methods are suggested and the relation between potential energy and interatomic distance of two non-bonded atoms is discussed. The values obtained in neutral solution are as follows: H, 0.95±0.1 Å; O (in C=O), 1.0±0.15 Å; and CH_3, 1.7±0.2 Å.

INTRODUCTION

The size of the hydrogen and other atoms in neutral solution is important for at least two reasons. First, it enables us to construct molecular models with correct interplanar angles. Secondly, values for a fixed set of conditions will aid the study of the relation of these interference values with temperature, concentration, pH, and dielectric constant of the solvent.

Yet the assignment of interference radii to various atoms in solution has been a subject of considerable discussion. Early attempts were made by Latimer and Rodebush (26), and Adams and Yuan (2) developed values based on substituted diphenyls. More recently Crombie (12) has proposed a value for the hydrogen interference radius of 0.75 Å, and Braude and Sondheimer (8) have used a value of 0.60 Å. The choice of these values rests on the belief that van der Waal's radii are too large a measure of steric hindrance in solution, and covalent radii too small. Covalent radii would not account for the large number of observed steric effects in solution (for example, those affecting the B-band of ultraviolet light absorption data (cf. Parts I, II, and III (16, 17, 20) of this series); van der Waal's radii cannot be used without modification since under the conditions discussed (that is, in neutral solution at room temperature) there may be some energy available inherent in these particular conditions. For example, a solution energy of say 5 kcal./mole may permit ready interaction of two atoms to within a distance which corresponds to a smaller interaction energy, say 1 kcal./mole.

A good illustration of this problem is provided by the diphenyl molecule. Electron diffraction measurements (4, 25), which give data about the isolated molecule, show diphenyl to be non-planar; the angle between the two rings has been reported as large as 45±10°, and the 1–1′ bond distance as 1.54 ±0.03 Å (25), corresponding to a carbon–carbon single-bond with little double-bond character. X-ray methods, on the other hand, show diphenyl to be planar in the crystalline state; with a 1–1′ bond distance of 1.48 Å, indicating appreciable double-bond character (14). This must be ascribed to forces prevailing in the crystalline state, sufficiently strong to overcome the interaction energies

[1]*Manuscript received May 23, 1956.*
Contribution from Memorial University of Newfoundland, St. John's, Newfoundland.

of the *ortho*-hydrogen atoms. (We are assuming that in the gaseous state there is a certain amount of steric hindrance because of mutual interaction of the *ortho*-hydrogen atoms. This seems reasonable, since it is difficult to postulate any other factor which would oppose the tendency of the resonance energy to keep the molecule planar.)

The particular problem for diphenyl is whether the molecule is planar or non-planar *in solution*. If it is planar, the effective interference value of the hydrogen atoms must be less than 0.90 Å; this is the value obtained for the two (assumed spherical) hydrogen atoms in a planar molecule just touching, using the accepted values for carbon–carbon and carbon–hydrogen distances and bond angles (14, 27). If the diphenyl molecule can be shown to be non-planar, the effective interference value of the hydrogen atoms must similarly be greater than 0.90 Å.

The more general problem may then be attempted thus: Having obtained from this and other examples a number of maximum and minimum values for the hydrogen and other atoms, these values can then be used to calculate interplanar angles, which in turn may be checked against other available data. The assumption is that the value for the effective interference radius of hydrogen will be similar for most molecules. This is not necessarily true and will be referred to again later; however, it will serve as a first approximation.

INTERFERENCE RADII FROM STERIC EFFECTS IN THE B-BANDS OF ABSORPTION SPECTRA

Steric effects in the B-bands of absorption spectra can be divided into three types, depending on the magnitude of the steric interaction (8, 16). The smallest amount of steric interaction detectable by this method gives rise to a steric effect of type I, namely a decrease of transition probability unaccompanied by a change in location of maximal absorption. The theoretical interpretation of this steric effect has recently been discussed (8, 18).

Since steric effects of type I have been ascribed to interaction between non-bonded atoms, we can use examples where steric effects of this type occur to calculate minimum interference values of non-bonded atoms which cause the steric interaction. Suitable examples of type I steric hindrance consequently represent the minimum steric interaction which may be detected directly from absorption spectra. Examples will be suitable if they indicate a steric effect beyond reasonable doubt. On the other hand the steric effect should not be too pronounced because a large steric effect represents a large interplanar angle; thus the minimum value based on a planar molecule will be considerably less than the actual interference value. This follows because the interference value is based on the assumption that the non-bonded atoms just touch; that is, the molecule is near-planar or only just planar. Further, bending effects have also been neglected which emphasize that values obtained represent minimum values. The two examples discussed are acetophenone and 2-methyl-benzaldehyde.

Acetophenone absorbs maximally at 240 mμ, ϵ = 12,500, while benzaldehyde under identical conditions absorbs maximally at 244 mμ, ϵ = 13,000 (16).

Since substitution of a $COCH_3$- for a CHO-group does not normally give a hypsochromic shift—for example CH_2=CH.CHO and CH_2=CH.$COCH_3$ absorb maximally at 206 (ϵ = 10,500) and 207.5 mμ (ϵ = 10,000) respectively under identical conditions (Bowden, Heilbron, Jones, and Weedon (6) report a maximal absorption of 210 mμ for methylvinyl ketone)—we may assume that acetophenone is sterically hindered with respect to benzaldehyde.* By means of a scale diagram of acetophenone we can thus obtain a minimum value for the effective interference radius of the hydrogen atom. This is illustrated in Fig. 1. It is necessary to consider the sterically less favorable conformation

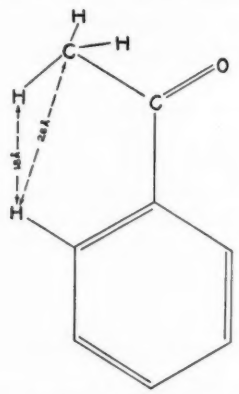

FIG. 1. Scale diagram of the less favorable planar configuration of acetophenone.

because conceivably the more favorable conformation may not contribute to the observed effect (cf. 18). The hydrogen value obtained by this method is 0.93 Å, in good agreement with the value obtained for a diphenyl molecule which is just planar. We can also use Fig. 1 to obtain directly a value for the effective interference radius of a methyl-group. The value thus obtained is 1.7 Å, identical with the value used by Braude and Sondheimer (8).

Concerning the *actual* interplanar angle of acetophenone, it is difficult to ascertain this with certainty, since it has been shown that small interplanar angles (up to 20°) will not affect the resonance interaction to any great extent (13, 22, 28). For acetophenone the interplanar angle is probably small; 4-methylacetophenone has been assumed planar (18) and although the absence of the methyl-group presumably lessens the coplanarity of the molecule (see below), the difference in interplanar angle is unlikely to be very appreciable.

A similar approach may be used for 2-methylbenzaldehyde which absorbs maximally at 251 mμ, ϵ = 13,000, while 4-methylbenzaldehyde under similar conditions absorbs maximally at 251 mμ, ϵ = 15,000 (8). If we then conclude that the spectrum of 2-methylbenzaldehyde exhibits a typical type I steric effect, and base our calculations on the sterically less favorable conformation, the scale diagram gives an interference value for the oxygen atom of 0.62 Å,

*We are indebted to Dr. J. S. Fawcett for suggesting this example to us.

or 0.85 Å, depending on whether the value H = 0.9 Å or CH_3 = 1.7Å is used. This value is almost certainly low because a planar molecule has been assumed whereas an estimate of interplanar angles (cf. 18) suggests an interplanar angle of 31° for the *s-cis* form of 2-methylbenzaldehyde. This would correspond to the much more likely interference radius of 1.1 Å for the carbonyl oxygen.

A further check may be obtained from the estimate of 50° for the interplanar angle of the *s-cis* form of 2-methylacetophenone. This leads to a value of 1.5 Å for the interference radius of the methyl-group.

Finally, in this section evidence ascribed to the "buttressing effect" may be used to confirm the proposed values. In molecules where both *ortho-* and *meta-*positions adjacent to an auxochrome are substituted, the steric effect is frequently enhanced relative to the *ortho*-substituted compound. Light absorption data indicate this buttressing effect to be due to steric rather than electronic causes (7, 16), an observation which is confirmed by the racemization rates of substituted diphenyls (1).

Using light absorption data to obtain interference radii, 2,3,5,6-tetramethyl- and 2,3,4,5,6-pentamethyl-acetophenones both exhibit distinct buttressing effects compared to the corresponding *meta*-unsubstituted reference compounds. The value thus obtained for the interference radius of the methyl-group is 1.47 Å, but this low value is not surprising since the steric effect as observed is quite appreciable (see 16). Consequently calculations based on the minimum detectable effect would lead to a larger value for the interference radius. This is in fact obtained, by considering interaction between a hydrogen atom and an adjacent methyl-group in the *meta*-position. The value for the interference radius of the methyl-group then obtained is 1.8 Å, assuming an interference radius of 0.9 Å for the hydrogen atom in a planar molecule. Spectral data actually indicate—since for example 3,3′-dimethyldiphenyl absorbs maximally at 255 mμ, ϵ = 16,500, while diphenyl itself absorbs maximally at 249 mμ, ϵ = 17,000 (7)—that a slight "buttressing-effect type" interaction occurs under these conditions; hence the value of 1.8 Å may provisionally be taken as another value obtained for the interference radius of the methyl-group.

THE NON-PLANARITY OF THE DIPHENYL MOLECULE AS EVIDENCED FROM TEMPERATURE EFFECTS ON THE SPECTRUM OF DIPHENYL

The ultraviolet absorption spectrum of diphenyl has been determined in the vapor phase between 170° and 520° C. (3). The data are recorded in Table I. Between 170° and 520° a bathochromic shift occurs accompanied by decreased absorption intensity at maximal wavelength. Using the schematic representations which have been found satisfactory in correlating various steric effects (18), it may be shown that a planar diphenyl molecule cannot account for the observed effect (i.e. a bathochromic shift), while a non-planar diphenyl molecule can account for the data (see Fig. 2).

In a planar diphenyl molecule (see Fig. 2(*a*)) increase of temperature (from T_1 to T_2 and to T_3) gives rise to progressive hypsochromic shifts as the mean transition energies become larger. Absorption associated with certain vibra-

TABLE I

LIGHT ABSORPTION CONSTANTS OF DIPHENYL (B-BANDS) IN THE VAPOR PHASE (3)

	(20° in hexane)	170°	260°	360°	520°
$\lambda_{max}(m\mu)$	$\simeq 245$	238.1	——→		239.5
ϵ_{max}	16,430	12,050	10,900	9900	9400

tional levels (for instance, at temperature T_3) will not necessarily always lead to actual transitions, but the increase of temperature will make transitions involving greater energy changes more probable, and thus further increase the mean transition energy. The absorption intensity may be expected at first to remain approximately constant as the temperature increases from T_1 to T_2, and then to decrease as the temperature approaches T_3, because potential electronic excitations from higher vibrational levels no longer lead to actual transitions.

In non-planar diphenyl molecules, as the temperature increases from T_1 to T_2 and T_3, the mean transition energy can become smaller and a *bathochromic* shift may be observed. For the extreme example illustrated in Fig. 2(*b*), the absorption intensity will remain approximately constant over the range T_1 to T_3.

A diphenyl molecule with an interplanar angle intermediate to those illustrated in Figs. 2(*a*) and (*b*), when the temperature is increased, may exhibit a hypsochromic shift followed by a bathochromic shift, or vice versa. However, a bathochromic shift indicates non-planarity, and the observed bathochromic shift therefore confirms the non-planarity of the diphenyl molecule in the vapor phase.

If we now assume that addition of hexane for the value at 20° will not appreciably affect the energy relationships of the ground state, we would have evidence concerning the non-planarity of the diphenyl molecule in solution. This supposition seems reasonable since *n*-hexane is an inert solvent and because dilution experiments (see Table II) indicate that association under these conditions is negligible.

TABLE II

THE ABSORPTION OF DIPHENYL AT DIFFERENT CONCENTRATIONS IN CYCLOHEXANE AND ABSOLUTE ETHANOL (21)

Solvent	Cell length (cm.)	Concentration (moles/l.)	λ_{max} ($m\mu$)	ϵ_{max}
Cyclohexane	0.1	2.6×10^{-4}	247	16,200
Cyclohexane	4	6.5×10^{-6}	246	15,600
Ethanol	0.1	2.8×10^{-4}	247	17,300
Ethanol	4	7.1×10^{-6}	246	17,300

Further, diphenyl absorbs in different solvents at approximately the same wavelength and intensity, which suggests the absence of the equivalent of

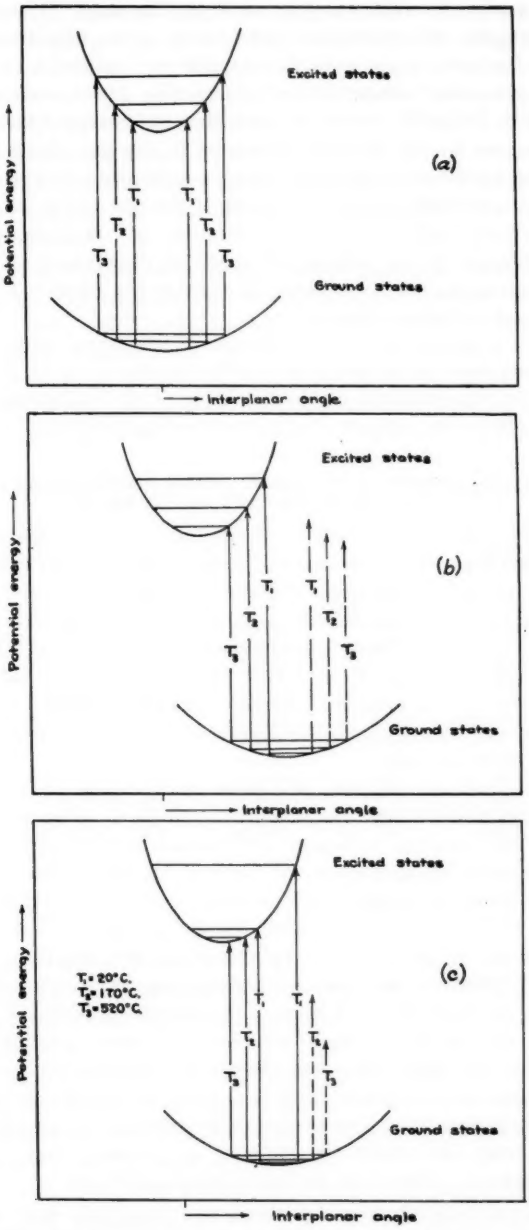

FIG. 2. Schematic representation of electronic transitions between ground and excited states in diphenyl; with (*a*) interplanar angle assumed to be zero, (*b*) interplanar angle assumed to be large, (*c*) actual interplanar angle.

lattice forces (as in the solid state) to overcome the steric interaction between the *ortho*-hydrogens. If such forces were present in the liquid state one would expect these forces to vary with the solvent and concentration. Hence the absence of appreciable solute–solvent interaction (as is indicated from the data reported in Table II) favors the view that the energy relationships in the solution phase are similar to those obtained in the gas phase, and is consequently opposed to the view that the energy relationships in the solution phase are necessarily intermediate between those of the gas and solid phases.

The very much higher absorption intensity at room temperature may readily be explained by an interplanar angle as illustrated in Fig. 2(*c*). The latter also summarizes our hypotheses concerning the electronic transitions of diphenyl at various temperatures.

The effect of temperature on the absorption spectra of various other compounds has been reported to give rise to different effects (5, 23, 24, 30); further work to correlate these effects with interplanar angles and solvent effects is in progress and will be the subject of a separate communication.

INTERFERENCE RADII AS DEDUCED FROM THE EFFECTS OF *PARA*-SUBSTITUENTS

This method arises as a possible development of a suggestion made by Braude and Sondheimer (8), who noted that a *para*-methyl substituent may either enhance or reduce the steric effect of an *ortho*-substituent. It was found that in 2,4,6-trimethylbenzaldehyde a *para*-methyl group reduces the *ortho*-effect, whereas in 2,4,6-trimethylacetophenone it enhances it. The suggestion of Braude and Sondheimer (8) was that the additional conjugation reduces the non-planarity of the system *if* steric hindrance is weak; if, however, the steric hindrance is large, the additional conjugation merely enhances the congestion at the acetyl group.

This follows since introduction of a *para*-methyl substituent increases the resonance energy and because the interplanar angle is determined essentially by an equilibrium between resonance and interaction energies. Hence a gain of resonance energy greater than the increase of steric interaction energy, caused by the bond shortening, will lead to a decreased interplanar angle. Conversely, if the increase in resonance energy is less than the gain in steric interaction energy, an increased interplanar angle will result.

The method therefore has distinct possibilities to determine, firstly, the onset of steric interaction (and hence the effective interference radii), and more generally the amount of steric interaction present, provided the gain in resonance energy is known. However, before it is possible to detect the onset of small decreases (due to steric interaction) in the over-all stabilization produced by the increased resonance energy, it is necessary to consider some other factors which may also affect the changes in intensity and wavelength of maximal absorption. These may be formulated as follows:

(i) The conjugating effect of a *para*-methyl group will vary depending on the amount of conjugation already present. For example, the effect would be expected to be larger in a medium such as sulphuric acid, where the stability

of dipolar contributing forms would be enhanced by the ionizing properties of the solvent. Similarly, if the auxochrome has a large negative *mesomeric* effect (for example, $—COCH_3$ or $—NO_2$), the change due to the *para*-methyl group would be expected to be greater than if the auxochrome has a small or a positive *mesomeric* effect (for example, $—CH_3$ or $—NH_2$; cf. also (19)).

(ii) The *para*-methyl group may change the amount of association between molecules. Association has been shown to vary when the molecular structure is modified even slightly (21) and this may consequently affect the wavelength and intensity changes.

(iii) *para*-Methyl substituents may increase the force constant of the bond linking the two planar entities. This will lead to less "shallow" potential energy curves throughout, but the change will be more pronounced in the excited than in the ground states.

We may now attempt to interpret the data recorded in Table III. It is noted that a number of compounds on *para*-methyl substitution exhibit batho-

TABLE III

CHANGES OBSERVED ON INTRODUCING A *para*-METHYL-GROUP IN A NUMBER OF AROMATIC SYSTEMS

Compound	Without *para*-methyl		With *para*-methyl			
	$\lambda_{max}(m\mu)$	$\epsilon_{max}(\epsilon_0)$	$\lambda_{max}(m\mu)$	ϵ_{max}	$\Delta\lambda$	ϵ/ϵ_0
Benzaldehyde[1]	242	14,000	251	15,000	9	1.07
Acetophenone[2]	243	13,200	252	15,100	9	1.14
Benzoic acid[3]	227	11,000	236	14,000	9	1.3
Toluene[4]	207.5	7,000	211	7,200	3.5	1.0
Nitrobenzene (in *iso*octane)[5]	252	8,600	264	10,300	12	1.2
Benzaldehyde (in H_2SO_4)[6]	293	21,000	309	23,000	16	1.1
Acetophenone (in H_2SO_4)[5]	295	28,000	311.3	30,000	16.3	1.1
Acetanilide[3]	242	14,500	245	15,000	3	1.0
Diphenyl[4]	247	17,300	250	17,700	3	1.0
2,6-Dimethylbenzaldehyde[1]	251	12,500	264	14,500	13	1.2
2-Methylacetophenone[2]	242	8,700	251	14,100	9	1.6
2,6-Dimethylacetophenone[2]	251	5,600	242	3,600	−9	0.6

[1]*Reference 8; in hexane.*
[2]*Reference 8.*
[3]*Reference 20.*
[4]*This paper.*
[5]*Reference 11.*
[6]*Reference 19.*

chromic shifts of about 9 mμ and an ϵ/ϵ_0 ratio of about 1.1. For compounds where the negative *mesomeric* effect of the auxochrome is large (for example, nitrobenzene) or for spectra in sulphuric acid solution, the wavelength change is much greater.

The slight change in the ϵ/ϵ_0 ratio from acetophenone to benzaldehyde may represent the known steric hindrance exhibited by the former; however, the data are insufficiently conclusive at this stage to permit a decision. Furthermore, minor steric interactions appear to give rise to a variety of effects. For example, steric interactions may give rise to an abnormally small positive wavelength shift, as from diphenyl to 4-methyldiphenyl; or it may lead to an abnormally large positive wavelength shift, as from 2,6-dimethyl- to 2,4,6-trimethyl-benzaldehyde; or again it may result in considerably in-

creased intensity of absorption, for example from 2-methyl- to 2,4-dimethyl-acetophenone (see Table III). Detailed discussion of these phenomena also will therefore be deferred for the present.

Another application of this method is that it may be used to calculate directly interaction energies from known interatomic distances between sterically interacting atoms. Thus, if on introducing a *para*-methyl group a negative wavelength change is observed, when a positive shift is normally obtained, then this change in wavelength will correspond to the steric interaction energy increase. For instance, we may assume that the gain of resonance energy on introducing a *para*-methyl substituent in both 2-methyl- and 2,6-dimethyl-acetophenone is approximately 9 mμ; since 2,4,6-trimethylacetophenone actually exhibits a hypsochromic shift of 9 mμ, the steric interaction will be equivalent to a wavelength change of about 18 mμ. This corresponds to 8 kcal./mole, and since we estimated the interplanar angle of 2,4,6-trimethylacetophenone to be 63° (which in turn corresponds to a distance of 3.2 Å between the two adjoining methyl-groups), we now obtain a value of 8 kcal./mole for two methyl-groups 3.2 Å apart.

This then represents one aspect, perhaps the most promising of the method, though evidently more subtle applications may become possible at a later stage.

CONCLUSIONS

The minimum interference values thus obtained are: hydrogen, 0.93, 0.90 Å; oxygen (in C=O), (0.62, 0.85), 1.1 Å; and methyl-group, 1.7, 1.5, (1.47), 1.8, 1.7 Å. Although the variation obtained is not too large (omitting the more doubtful bracketed values), it must be remembered that the effective interference radius of an atom will not be constant under different conditions. This variation may depend on a number of factors, such as:

(*a*) the type of covalent bond involved;

(*b*) the nature of the opposing (interfering) partner;

(*c*) the direction of maximum interference relative to the direction of its valency;

(*d*) the temperature;

(*e*) the degree of association with solvent molecules;

(*f*) the pH of the solvent;

(*g*) the dielectric constant of the solvent.

In the present communication only similar benzenoid compounds are discussed in order to reduce the number of variables to a minimum (9, 10, 27).

To obtain a maximal value for interference radii we again use the example of diphenyl, assuming that the maximum intensity of absorption of a completely planar diphenyl molecule is not higher than 42,000. This value is taken as more than twice the intensity value at room temperature since instances are known where on reducing the temperature from 20° C. to about −200° C. the intensity of absorption is almost doubled (cf. 5); this change may—although this is unlikely—be ascribed entirely to increased planarity at lower temperature. Using the equation $\epsilon/\epsilon_0 = \cos^2\theta$ (8, 18) where $\epsilon_0 = 42{,}000$, for calculating the interplanar angle in 2-methyldiphenyl which absorbs maximally

at 235 mμ (i.e. at similar wavelength compared to diphenyl) with $\epsilon = 10{,}500$ (7), we obtain a maximum interplanar angle of 60°. This leads to an interatomic distance of 2.86 Å between the hydrogen atom and the methyl-group, which corresponds to maximal values for hydrogen of 0.99 Å and 1.87 Å for the methyl-group (it is assumed that the maximum values are proportional to the minimum values).

The maximum value of 60° for the interplanar angle also appears reasonable, since it has been assumed (22) that at an angle of 67.5° there will be no conjugation between the two planar entities of the diphenyl molecule. 2-Methyldiphenyl, however, still exhibits some conjugation as compared to, for example, 2,2′-dimethyldiphenyl which only has an inflection at 227 mμ, $\epsilon = 6800$, indicating almost complete loss of cross-conjugation.

Using a similar argument for benzaldehydes—namely assuming an intensity of absorption for a planar benzaldehyde molecule of $\epsilon = 28{,}000$—we can calculate the maximum interplanar angle of 2,6-dimethylbenzaldehyde (which absorbs with $\epsilon = 12{,}500$ at comparable wavelength to benzaldehyde) to be 48°. This leads to a maximum interference value of 1.15 Å for oxygen (in C=O), using the previously obtained value of 1.7 Å for the methyl-group.

The final values therefore suggested for the effective interference radii are as follows:

H, 0.95±0.1 Å;
O (in C=O), 1.0±0.15 Å;
CH_3, 1.7±0.2 Å.

EXPERIMENTAL PART

Redistilled toluene had a boiling point of 111°, n_D^{20} 1.4960; *p*-xylene had a melting point of 13°. After fractionation under nitrogen, acrolein distilled at 52°, 769 mm., n_D^{20} 1.3998, and methylvinyl ketone at 34°, 130 mm., n_D^{20} 1.4086; 4-methyldiphenyl had a melting point of 45°. Methylvinyl ketone was prepared by the method of Wohl and Prill (29) and 4-methyldiphenyl by the method of Elks, Hayworth, and Hey (15).

The light absorption properties of the above-described compounds are recorded in Table III. The spectra were determined in duplicate by standard methods with 1 cm. cells using a Unicam SP500 spectrophotometer. Spectra, unless otherwise stated, are recorded in ethanolic solution. The determinations involving acrolein and methylvinyl ketone were carried out by direct addition of the substances to a known amount of solvent; the mixture was then diluted to the required concentration and the absorption intensity at maximal wavelength determined as quickly as possible.

ACKNOWLEDGMENTS

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They are also greatly indebted to the late Professor E. A. Braude for a number of discussions related to this general topic.

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AN EXPERIMENTAL DETERMINATION OF THE SURFACE ENTHALPY OF SODIUM CHLORIDE[1]

By G. C. Benson, H. P. Schreiber,[2] and F. van Zeggeren[3]

ABSTRACT

The surface enthalpy of NaCl has been redetermined from heats of solution of salt samples of different specific surface areas. Special care was taken in the preparation of these samples to avoid contamination by nitrate and excess sodium. The value obtained, 276 ergs/cm.^{2}, differs from that reported by Benson and Benson, viz. 305 ergs/cm.^{2}, for samples containing some nitrate impurity.

INTRODUCTION

Recently Benson and Benson (1) determined the surface enthalpy of sodium chloride by measuring heats of solution for samples of varying specific surface area. The differences of these heats of solution from that of bulk sodium chloride, when plotted as a function of the surface area, gave a straight line indicating that the deviation could be considered as a surface property to a good approximation. The slope of the least square line through the points obtained led to a value of 305 ergs/cm.^{2} for the surface enthalpy at 298° K. and this was attributed to the {100} face of the crystal. However, the line also had a negative intercept of −5.4 cal./mole which appeared to be due to some impurity in the fine salt. Prior to this, the only indications of contamination noted were the occurrence of a slight blue color in some samples and an alkaline pH for solutions of these samples in water, both suggesting the presence of excess sodium in the lattice. Since material of this kind was not used for the calorimetric measurements the negative intercept could not have been due to non-stoichiometric sodium. Furthermore, in view of the sign of the intercept, the impurity most probably had a negative heat of solution in water. It was found that material used in the calorimetric work gave a positive spot test for nitrite or nitrate. Further investigations (11) have confirmed the presence of sodium nitrate in material prepared under similar conditions.

The heat of solution of sodium nitrate in water is negative and since its magnitude is roughly four times that of sodium chloride, the percentage of sodium nitrate present in the fine salt used by Benson and Benson appears to have been relatively small (about 0.3%). Since the various specific surface areas were obtained by sintering the same starting material, a small amount of nitrate would probably have little effect on the slope of the line provided it was uniformly distributed through the bulk of the particles. On the other hand if there was a tendency for the impurity to concentrate in the surface, some influence on the surface enthalpy is quite conceivable, and the value reported by Benson and Benson was stated to be provisional. In the present paper a redetermination of the surface enthalpy of sodium chloride is described.

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Contribution from the Division of Pure Chemistry, National Research Council, Ottawa, Canada. Issued as N.R.C. No. 4072.
[2]*National Research Laboratories Postdoctorate Fellow 1953–55. Present address: Central Research Laboratories, Canadian Industries Limited, McMasterville, Quebec.*
[3]*National Research Laboratories Postdoctorate Fellow 1955–.*

EXPERIMENTAL

The fine salt was prepared as in previous work by the electrostatic precipitation of a sodium chloride smoke. The occurrence of nitrate and excess sodium in the product has been studied by van Zeggeren, Schreiber, and Benson (11). Two factors which play an important role in the formation of these impurities are the oxygen content of the carrier gas and the precipitator voltage. In the present work a nitrogen carrier gas containing 0.05% oxygen and a precipitator voltage of 8 kv. were used. As stated in Reference 11 these conditions lead to a nitrate content of less than 0.05%. Checks were also made on the alkalinity of the salt.

Most of the samples with different surface areas were obtained from 12 independent preparations but a few of the low area samples were made by the thermal sintering of higher area material. Determinations of the surface areas were carried out according to the B.E.T. method and the values are based on a nitrogen molecular area of 16.2 Å². Most of the isotherms obtained for nitrogen on sodium chloride gave slightly curved B.E.T. plots in the usual p/p_0 range (0.05 to 0.3) and led to small negative intercepts when fitted with a line in this region. Points in the p/p_0 range 0.01 to 0.1 gave linear B.E.T. plots with small positive intercepts and this pressure region was used for the area

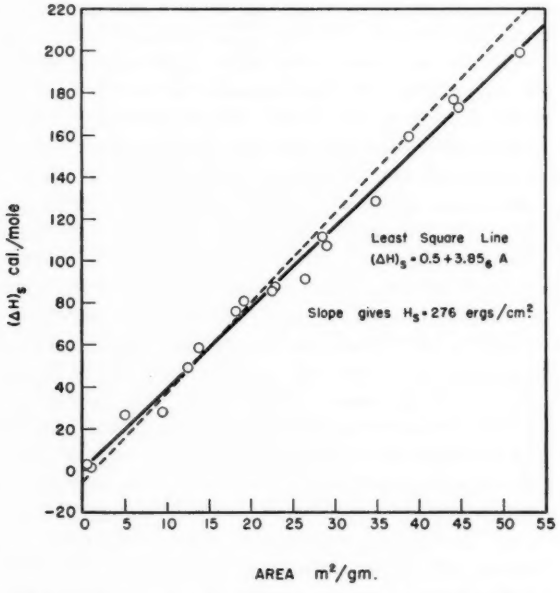

FIG. 1. Plot of the variation of the ΔH for solution of sodium chloride in water at 25° C. as a function of the surface area of the sample. The solid line drawn through the new data corresponds with a surface enthalpy of 276 ergs/cm.² For comparison the results obtained in Reference 1 are indicated by the dashed line, the slope of which corresponds with a surface enthalpy of 305 ergs/cm.²

determinations in the present work rather than the range 0.05 to 0.3 employed previously.* The effect of this change on the area is relatively small.

The calorimetric techniques used were the same as described in References 1 and 2. The deviation, $(\Delta H)_s$, of the enthalpy of solution of fine salt from that of bulk material has been plotted as a function of the specific surface area in Fig. 1.

DISCUSSION

The least square line through the points of Fig. 1 has an intercept of +0.5 cal./mole. The probable error of this intercept, calculated from the formulae of Birge (4), is 1.8 cal./mole, which indicates that now the line can be considered to pass through the origin within the experimental error. For the contaminated salt Benson and Benson (1) reported a value −5.4 cal./mole for $(\Delta H)_s$ at zero area, with a probable error of 2.4 cal./mole. This corroborates the view that in the present experiments the sodium nitrate content of the salt was negligible. The slope of the least square line corresponds with a surface enthalpy of 276 ergs/cm.^{2}, that is about 30 ergs/cm.^{2} less than the value obtained by Benson and Benson. Since the probable error in the new result is 5 ergs/cm.^{2} and in the previous work was 6 ergs/cm.^{2}, this difference is significant and it favors the possibility suggested in the introduction that the nitrate tends to concentrate in the surface regions rather than being uniformly distributed throughout the bulk of the crystals.

The new value is still much higher than the results of theoretical calculations. Recently van Zeggeren and Benson (10) obtained a value of 187 ergs/cm.^{2} as a first approximation for the surface energy of a {100} face of sodium chloride at 0° K. from a quantum mechanical model in which no allowance was made for van der Waals forces or distortion at the surface. A theoretical estimate of the surface energy on the basis of a classical model is 112 ergs/cm.^{2} at 0° K. This is taken from calculations by Shuttleworth (9) with the distortion energy contribution corrected in accordance with the findings of Benson, Schreiber, and Patterson (3).

It is unlikely that the difference in temperature can account for the deviation between the experimental result for 298° K. and theoretical values calculated for 0° K. Morrison and Patterson (7) have extended the temperature range of the specific heat measurements on finely divided sodium chloride previously reported by Patterson, Morrison, and Thompson (8). Their data show a definite particle size effect but it is not simply related to the surface area of the sample and these authors suggest that the excess specific heat over that predicted by the theoretical treatment of Montroll (6) is due to a loosening of the surface structure. Until this is investigated more completely, use of the data to estimate a temperature correction of the surface enthalpy is uncertain, but a decrease of 10 to 20 ergs/cm.^{2} would appear to be an upper limit for this correction.

Recently one other experimental determination of the surface enthalpy of

*We are most indebted to Dr. P. H. Emmett and Dr. S. Brunauer for discussions and correspondence which led to the change adopted here.

sodium chloride has been reported. Hutchinson and Manchester (5) obtained a value of 366 ergs/cm.^{2} from heats of solution of lyophilized salt. This result is rather uncertain since the surface area was estimated in an approximate manner from electron micrographs and no attempt was made to establish that the difference in the heats of solution was proportional to the specific surface area.

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SOME BASIC DERIVATIVES OF 6-CHLOROQUINAZOLINE AND PHTHALAZINE[1]

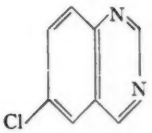
By Stanley O. Winthrop, Stella Sybulski, Roger Gaudry, and Gordon A. Grant

ABSTRACT

Basic derivatives of 6-chloroquinazoline and phthalazine have been synthesized and screened for their physiological action on the central nervous system. Sodium dialkylaminoalkoxides and the appropriate chlorobenzodiazine were brought together to yield basic ethers of 6-chloroquinazoline and phthalazine respectively. 1-(γ-Dimethylaminopropylamino)phthalazine was also prepared.

INTRODUCTION

This study represents a part of a continuing program which, it is hoped, will lead to new drugs acting on the central nervous system. It was of interest to investigate certain benzodiazine ring systems as possible carriers of groupings known to have central nervous system activity. We have investigated 6-chloroquinazoline (I) and phthalazine (II) as possible carriers of this type. The 6-chloroquinazoline was chosen rather than quinazoline itself because of its structural relationship to 3-chlorophenothiazine, a highly successful carrier.



I

II

Sherrill (1) has described the 4-(β-diethylaminopropoxy)-6-chloroquinazoline as its phosphate salt. We were unable to prepare this phosphate but found the citrate to be a more easily obtained acid addition salt. In an analogous manner, three new 6-chloroquinazoline basic ethers were prepared and are listed in Table I.

Although 1-alkoxyphthalazines have been reported (2), no mention of a 1-dialkylaminoalkoxyphthalazine could be found in the literature. The 1-(γ-diethylaminopropoxy)phthalazine was prepared from 1-chlorophthalazine and the appropriate alcohol by the same procedure as was used for the preparation of the quinazoline ethers.

The instability of phthalazines and particularly aminophthalazines towards heat has been noted. Only a small number of 1-alkylaminophthalazines have been reported (2) and their preparation usually results in resinous by-products and consequently low yields of the aminophthalazine. 1-(γ-Dimethylamino-

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Contribution from the Research Laboratories, Ayerst, McKenna & Harrison Limited, Montreal, Que.

TABLE I

6-CHLOROQUINAZOLINES

4-Substituents	Salt	M.p., °C. (uncorr.)	Yield,[e] %	Formulae	Carbon		Hydrogen		Nitrogen		Chlorine	
					Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
$(CH_3CH_2)_2NCH_2CH_2CH_2O$	Citrate	120–121[a]	41	$C_{21}H_{23}N_3O_3Cl$	51.88	51.95	5.81	5.77	8.65	8.91	7.31	7.19
$((CH_3)_2CH)_2NCH_2CH_2OCH_2CH_2O$	HCl	123–125[b]	34	$C_{18}H_{29}N_3O_2Cl_2$					10.82	10.80	18.26	18.28
$(CH_3CH_2)_2NCH_2CH_2OCH_2CH_2O$	$2H_2SO_4$	135–137[c]	24	$C_{16}H_{26}N_3O_{10}S_2Cl$	36.90	37.31	5.04	5.02	8.08	8.23	6.82	7.07
$(CH_3)_2NCH_2CH_2OCH_2CH_2O$	Maleate	111–112[b]	20	$C_{18}H_{22}N_3O_6Cl$	52.50	52.26	5.39	5.62	10.21	10.30	8.62	8.65
$(CH_3)_2NCH_2CH_2OCH_2CH_2O$		Oil[d]	52	$C_{14}H_{18}N_3O_2Cl$					14.22	14.18		

[a]*Recrystallized from isopropanol.* [b]*Recrystallized from ethylacetate.* [c]*Recrystallized from isopropanol–ether.* [d]*The base was obtained by treatment of the maleate salt with sodium carbonate solution followed by chloroform extraction. Removal of the chloroform and high vacuum drying gave a heavy oil which analyzed correctly for the free base.* [e]*The yields are based on the product as its salt after one recrystallization.*

propylamino)phthalazine was prepared from 1-chlorophthalazine and dimethylaminopropylamine. The presence or absence of a solvent did not appreciably affect the yields.

Some of the quinazolines were found to be central nervous system depressants and also showed appreciable musculotropic activity.

EXPERIMENTAL

4,6-Dichloroquinazoline

This was prepared from 5-chloroanthranilic acid by way of the 6-chloro-4-quinazolone (1). The material melted at 155–158°C. (lit. m.p. 154–155°C.).

1-Chlorophthalazine

Phthalaldehydic acid (Eastman) and hydrazine gave 1-hydroxyphthalazine which was in turn converted to 1-chlorophthalazine (2) by the action of phosphorus oxychloride. The compound melted at 114.5–115.5°C. (lit. m.p. 113°C.). 1-Chlorophthalazine had to be used fresh since it underwent a gradual transformation, on standing at room temperature, into higher melting substances.

4-(β-Dialkylaminoethoxyethoxy)-6-chloroquinazolines

The 4,6-dichloroquinazoline was allowed to react with sodium β-dialkylaminoethoxyethoxide in an excess of the aminoalcohol according to the method of Sherrill (1). The products were isolated as their acid addition salts since losses due to decomposition during an attempted vacuum distillation of one of the crude bases were excessive.

1-Dialkylaminoalkoxyphthalazines

The phthalazine basic ethers were prepared in the same manner as the quinazolines. The salts were heat sensitive and partly resinified on recrystallization. In some cases this causes losses of up to 50% and made purification difficult.

1-(γ-Dimethylaminopropylamino)phthalazine

Method A

1-Chlorophthalazine, 7.5 gm., 0.045 mole, and 9.2 gm., 0.09 mole, dimethylaminopropylamine were dissolved in 75 ml. of absolute alcohol and warmed on a water bath at 70°C. for seven hours. On cooling and addition of ether, dimethylaminopropylamine hydrochloride precipitated and was filtered off. The filtrate was evaporated down *in vacuo* at room temperature, leaving 10 gm. of a heavy oily residue. Ethereal hydrogen chloride was carefully added to an ether solution of the oil residue and the product precipitated as the dihydrochloride, 3.7 gm., m.p. 246–248°C. Two recrystallizations from ethanol–ether gave 1.4 gm. of a hygroscopic dihydrochloride, m.p. 242–243°C. (see Table II).

Method B

1-Chlorophthalazine, 7.5 gm., 0.045 mole, and 18.4 gm., 0.18 mole, dimethylaminopropylamine were warmed together on a water bath at 70°C. for

TABLE II

PHTHALAZINES

1-Substituents	Salt	M.p., °C.[a] (uncorr.)	Yield,[b] %	Formulae	Carbon		Hydrogen		Nitrogen		Halogen	
					Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
$(CH_3CH_2)_2NCH_2CH_2CH_2O$	Citrate $.H_2O$	129.5–130.5[d]	10	$C_{21}H_{31}N_3O_9$	53.65	53.95	6.65	6.61	8.94	9.07		
$(CH_3CH_2)_2NCH_2CH_2CH_2O$	$2CH_3I$	168.5–169.5[e]	21	$C_{17}H_{27}N_3OI_2$					7.75	7.93	46.73	46.13
$((CH_3)_2CH)_2NCH_2CH_2OCH_2CH_2O$	2HCl	118–120[f]	16	$C_{18}H_{29}N_3O_2Cl_2$					10.78	10.99		
$((CH_3)_2CH)_2NCH_2CH_2OCH_2CH_2O$	$2CH_3I$	163–165[e]	17	$C_{20}H_{33}N_3O_2I$					6.99	7.14	42.24	42.00
$(CH_3)_2NCH_2CH_2CH_2NH$	2HCl	242–243[e]	27	$C_{13}H_{20}N_4Cl_2$[c]	51.43	51.05	6.65	7.07			23.42	22.95
$(CH_3)_2NCH_2CH_2CH_2NH$	$2CH_3I$	235–237[e]	27	$C_{16}H_{26}N_4I_2$					10.58	10.56	48.05	48.17

[a] *Melting points were determined by placing the compound in the bath 15 degrees below the approximate melting point and increasing the temperature 2 degrees a minute. Variations in melting points occurred depending on the method used since the phthalazines are heat sensitive.* [b] *The yields are based on the product as its salt after one recrystallization. The yields before purifications were considerably greater than these recorded here.* [c] *This compound was very hygroscopic. Karl Fischer's analysis gave 6.02% water. The analyses are based on the dry weight.* [d] *Recrystallized from methanol–ether.* [e] *Recrystallized from ethanol–ether.* [f] *Recrystallized from isopropanol–ether.*

seven hours. The reaction mixture was then taken up in isopropanol–ether and the dimethylaminopropylamine hydrochloride precipitated. The filtrate was worked up as in Method A and the excess amine removed by vacuum distillation at 3 mm. The pot residue, a reddish oil, 11.1 gm., was taken up in acetone and treated with methyl iodide to yield 10.4 gm. of a bismethiodide salt, m.p. 236–238°C. Two recrystallizations from ethanol–ether gave 5.8 gm. of an analytically pure compound, m.p. 235–237°C.

ACKNOWLEDGMENTS

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AN IMPROVED SYNTHESIS OF ACETOSYRINGONE[1]

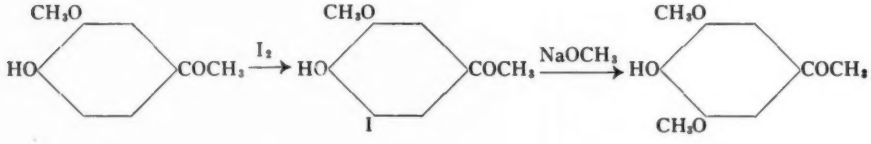
By L. W. Crawford, E. O. Eaton, and J. M. Pepper

ABSTRACT

Acetosyringone has been synthesized from acetovanillone, in better than a 50% yield, through conversion to 5-iodoacetovanillone followed by its interaction with sodium methoxide in the presence of copper catalyst. The previously unreported intermediate, 5-iodoacetovanillone, was characterized by methylation to 5-iodoacetoveratrone and subsequent oxidation to the known 5-iodoveratric acid.

One of the more fruitful fields of research on the chemical structure of lignin has been that of oxidation (3). By means of the alkaline nitrobenzene oxidation of wood meal itself, or of isolated lignins, good yields of the phenolic aldehydes vanillin and syringaldehyde have been obtained, along with lesser amounts of acetovanillone* (4-hydroxy-3-methoxyphenyl methyl ketone) (I) and acetosyringone* (4-hydroxy-3,5-dimethoxyphenyl methyl ketone) (III). With respect to the structure of lignin the latter two derivatives, being C_6—C—C fragments, are of more structural significance than the former more highly degraded C_6—C derivatives. In order to study the problems associated with the separation of these four lignin derivatives from admixture, it was necessary to have available pure samples of each compound. Vanillin and acetovanillone are available commercially and syringaldehyde may be synthesized by any of several methods (1, 11, 10, 13), but the reported syntheses of acetosyringone have been difficult and have resulted in poor over-all yields. The present work describes an improved two-stage synthesis of acetosyringone from acetovanillone.

Synthetic acetosyringone was reported first by Bradley and Robinson (2), who used a multistep synthesis starting from O-benzylsyringoyl chloride and ethyl acetoacetate, and who reported that their product melted at 117°C. Later, Mauthner (8) described the more direct synthesis involving the aluminum chloride catalyzed rearrangement of 2,6-dimethoxyphenyl acetate. Leger and Hibbert (7) and later Pepper and Hibbert (12) used this method of Mauthner and prepared acetosyringone melting at 120.5–121.5°C. and 121–122°C. and in yields of 11 and 12.6% respectively. A new synthesis has been effected starting from acetovanillone (I) according to the following equations:



I II III

[1]*Manuscript received June 25, 1956.*
Contribution from the Department of Chemistry, University of Saskatchewan, Saskatoon, Sask.

**The names acetovanillone and acetosyringone and those of their corresponding derivatives are used extensively in the literature and hence are used throughout this paper.*

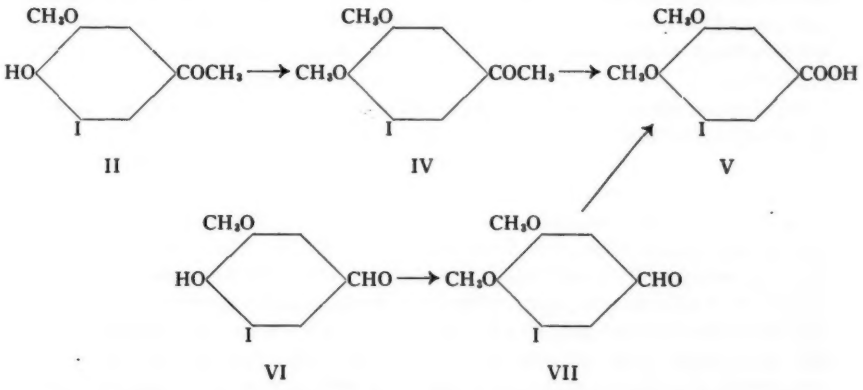
PLATE I

FIG. 7.

The procedure of Carles (4) for the iodination of vanillin, involving the addition of a methanolic solution of iodine to a warmed aqueous solution of vanillin, was applied to the iodination of acetovanillone, and a product obtained in 5.6% yield, after recrystallization from acetic acid, m.p. 175–177°C. A modification of the procedure used by Erdtman (5) for the synthesis of 5-iodovanillin, whereby the sodium hydroxide was replaced by sodium carbonate, gave rise to an iodinated derivative, in 82.5% yield, m.p. 172–174°C. No depression of melting points was found in admixture of samples of the iodinated products made by the two methods.

Since 5-iodoacetovanillone was previously unreported, it was first necessary to prove the structure of the iodinated product. The position of the ring-substituted iodine could be proved if the unknown were oxidized to a product identical with an authentic sample of 5-iodovanillic acid. All attempts to isolate 5-iodovanillic acid from the alkaline liquors of either sodium hypoiodite or sodium hypobromite oxidations were unsuccessful. Fuson and Bull (6) have reported that haloform reactions on either hydroxy- or nitro-acetophenones do not result in formation of the expected acids even though the haloform itself may be formed. Attempts to oxidize 5-iodovanillin by the method of Pearl (9), using silver oxide, were also unsuccessful.

The following series of reactions served to characterize the unknown as 5-iodoacetovanillone.



The unknown was converted by methylation to 5-iodoveratryl methyl ketone (IV) and hence to 5-iodoveratric acid (V) by oxidation with potassium permanganate. This last compound was identical with a sample of the acid prepared by the methylation of 5-iodovanillin (VI) to 5-iodoveratraldehyde (VII) followed by oxidation.

The 5-iodoacetovanillone was then converted to acetosyringone (III) by a procedure similar to that whereby 5-iodovanillin had been converted to syringaldehyde (13), i.e. by the interaction with methanolic sodium methoxide at elevated temperatures in the presence of copper catalyst. The crude acetosyringone was purified by recrystallization from water. The results of six such experiments are given in Table I.

TABLE I

REACTION OF 5-IODOACETOVANILLONE WITH SODIUM METHOXIDE USING COPPER CATALYST

Run	Temp., °C.	Time, hr.	MeOH-sol.,* gm.	Acetosyringone			
				From water		From mother liquor	
				Wt., gm.	M.p., °C.	Wt., gm.	M.p., °C.
1	149–151	1	8.0	4.1	116–123	1.5	60–90
2	141–144	1	8.8	4.9	113–120	1.8	65–110
3	133–135	1	10.0	4.1	110–121	—	—
4	135	†	6.0	1.5	115–120	2.2	98–105
5	136–139	0.5	8.2	2.7	115–121	3.2	98–110
6	135–137	4.75	10.0	4.0	119–122	1.0	119–123

Theoretical yield of acetosyringone, 9.4 gm.
†*Reaction mixture heated to 135°C., then cooled immediately.*

EXPERIMENTAL

All melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected.

Synthesis of 5-Iodoacetovanillone

(*a*) Acetovanillone (5.1 gm.) was dissolved in water (100 ml.) and a solution of iodine (3.0 gm.) in methanol (100 gm.) was added. The mixture was well stirred and maintained at a temperature of 50°C. for 24 hr. After the mixture was cooled, the resultant precipitate was removed by filtration and was recrystallized from acetic acid, to yield a product (0.5 gm., 5.6%), m.p. 175–177°C.

(*b*) Acetovanillone (50 gm.) and sodium bicarbonate (16.0 gm.) were dissolved, with warming, in water (300 ml.). To this a solution of iodine (75.6 gm.) dissolved in a solution of potassium iodide (85.0 gm.) in water (400 ml.) was added slowly with stirring whilst the temperature was maintained at 80°C. After the addition of approximately 25% of the iodine solution a yellow precipitate appeared. After complete addition, the resultant solution was decolorized with a minimum quantity of sodium thiosulphate and filtered while hot. After the precipitate collected, it was washed with water (500 ml.) and dried; yield 72.5 gm., 82.5%, m.p. 172–174°C. After recrystallization of the precipitate from ethanol–water, then ethanol, the melting point was 178–179°C. Calc. for $C_9H_9O_3I$: C, 37.00; H, 3.11%. Found: C, 37.02; H, 3.11%. The *p*-nitrophenylhydrazone melted at 212–213°C. A mixed melting point with the sample prepared by Carles' method gave no depression.

Characterization of 5-Iodoacetovanillone. 5-Iodoveratraldehyde

5-Iodovanillin (3 gm.) and sodium bicarbonate (20 gm.) were heated in water (100 ml.) to 55°C. Dimethyl sulphate (6.7 gm.) was added dropwise during one half hour, the temperature being maintained at 55°C. On cooling, the mixture was extracted with ether (100 ml.), and the ether extract washed with *N* sodium hydroxide, dried, and concentrated to yield white crystals; yeild 1.24 gm., m.p. 70–72°C.; reported m.p. 72–73°C. (14).

5-Iodoveratric acid from 5-iodoveratraldehyde.—5-Iodoveratraldehyde (1.24 gm.) was added to pyridine (6 ml.) and the mixture maintained at 55°C. during the slow addition of potassium permanganate (5%, 8 ml.). After removal of the precipitated manganese dioxide, the filtrate was discolored with a little sodium bisulphite, poured into water, and acidified with concentrated hydrochloric acid. The crude product that precipitated (0.67 gm., 51%), m.p. 179–180°C., was purified by reprecipitation, by acidification, from an ether-extracted alkaline solution; m.p. 183–183.5°C.; reported m.p. 184–185°C. (13).

5-Iodoacetoveratrone.—A solution of 5-iodoacetovanillone (1.2 gm.), dimethyl sulphate (2.7 gm.), and ethanol (7 ml.) was heated to reflux. Sodium hydroxide (10 *N*, 3 ml.) was added dropwise over a period of 15 min. After the further addition of dimethyl sulphate (2.7 gm.), sodium hydroxide (10 *N*, 3 ml.), the mixture was refluxed for one-half hour and poured into water (200 ml.). The alkaline solution was extracted with ether (2 × 50 ml.); the extract, after drying and concentration, yielded crude 5-iodoacetoveratrone, 1.0 gm. (79%), m.p. 73–77°C. Recrystallization from ethanol–water, then ethanol, gave white crystals, m.p. 78–79°C. Calc. for $C_{10}H_{11}O_3I$: C, 39.23; H, 3.62%. Found: C, 39.17; H, 3.64%. No previous report on this compound could be found.

5-Iodoveratric acid from 5-iodoacetoveratrone.—5-Iodoacetoveratrone (1.0 gm.) was dissolved in pyridine (10 ml.) and the mixture heated to 60°C. during the addition of potassium permanganate (5%, 30 ml.) in 5 ml. portions. After removal of the manganese dioxide, the filtrate was discolored with sodium bisulphite, made alkaline with sodium hydroxide, and extracted with ether. The aqueous layer, after acidification, was extracted with ether (100 ml.). From this extract, after drying and concentration, 5-iodoveratric acid was obtained (0.33 gm., 33%), m.p. 183–184°C. A mixed melting point determination on samples of the acid made by both methods showed no depression.

Acetosyringone

A typical synthesis is as follows: Sodium (12 gm.) was dissolved in anhydrous methanol (300 ml.) and this solution together with copper powder (B.D.H. precipitated, 7.7 gm.) and 5-iodoacetovanillone (14 gm.) was heated, with shaking, in a bomb, capacity 1410 ml., of an Aminco high pressure hydrogenator, Model No. 406-01DA. Temperature control was ±4°C. At the end of the specified reaction time the bomb was cooled and the contents rinsed into a beaker with water (600 ml.) The copper catalyst was removed by filtration and the filtrate acidified with concentrated hydrochloric acid. This precipitated any unchanged 5-iodoacetovanillone, which was much less soluble, *ca.* 1/200, than the required acetosyringone. The filtrate was extracted with chloroform (6 × 200 ml.) and the extract was then washed with 5% sodium thiosulphate (100 ml.), then with water (2 × 100 ml.), and finally evaporated under reduced pressure to dryness. The residue was extracted with methanol (100 ml.) whereby some red colored impurities were separated as a methanol-insoluble portion. Evaporation of the methanol gave the crude acetosyringone, which was crystallized from water. A sample recrystallized

from water, then Skellysolve "C", melted at 123–124°C.; reported m.p. 121–122°C. (12). Calc. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17%. Found: C, 61.40; H, 6.14%. The *p*-nitrophenylhydrazone melted at 193.5–194.5°C.; reported m.p. 194.5–195.5°C. (7).

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1-(β-DIALKYLAMINOETHYL)-2-IMIDAZOLIDINETHIONES[1]

By A. F. McKay, D. L. Garmaise, and A. Halasz

ABSTRACT

A series of 1-(β-dialkylaminoethyl)-2-imidazolidinethiones and their picrates are described. 1-(β-Diethylaminoethyl)-2-methylmercapto-2-imidazoline dihydroiodide combined with benzylamine with the evolution of methyl mercaptan to give 1-(β-diethylaminoethyl)-2-benzylamino-2-imidazoline (III). In a similar reaction β-alanine gave a product whose picrate gave analytical values in agreement with those calculated for the dipicrate of 1-(β-diethylaminoethyl)-5-keto-Δ^3-hexahydro-1,4,8-pyrimidazole (IV).

Recently the preparation and properties of a series of 1-alkyl-2-imidazolidinethiones were described by Thorn (11). A similar method of preparation has been used to prepare 1-(β-hydroxyethyl)-2-imidazolidinethione (8), 1-isopropylhexahydropyrimidine-2-thione (7), and a series of 1-(β-dialkylaminoethyl)-2-imidazolidinethiones. The 1-(β-dialkylaminoethyl)-2-imidazolidinethiones and their picrates are described in Table I. During the course of this work 1-isopropoxypropyl-2-imidazolidinethione also was prepared.

The amines required for the syntheses of the 1-(β-dialkylaminoethyl)-2-imidazolidinethiones were prepared by the addition of ethylenimine to the corresponding dialkylamines (4, 5). The properties of these amines and their picrates are given in Tables II and III respectively.

1-(β-Diethylaminoethyl)-2-imidazolidinethione was converted to its hydroiodide salt (I) and then methylated with methyl iodide. This procedure eliminated the possibility of methylating the diethylamino group and 1-(β-diethylaminoethyl)-2-methylmercapto-2-imidazoline dihydroiodide (II) was obtained in good yield (92.5%). Compound II on refluxing with 1 mole equivalent of benzylamine in the presence of methanol evolved methyl mercaptan. The product on treatment with aqueous picric acid gave a dipicrate melting at 210–211°C. This picrate on analysis gave values in good agreement with the dipicrate salt of structure III ($R = C_6H_5CH_2$). This reaction is analogous to previously described reactions of amines with 2-methylmercapto-2-imidazolines (2, 7, 8) and 2-methylmercapto-2-oxazolines (10).

Several attempts to prepare 1-(β-diethylaminoethyl-2-(β-carboxyethyl)-2-imidazoline by the reaction (6, 7) used in the synthesis of cyclic guanidino acids gave variable results. In some runs large amounts of unreacted β-alanine were recovered. Three runs produced a viscous oil which on treatment with aqueous picric acid gave a picrate melting at 176.5–177°C. This compound gave analytical values in excellent agreement with the calculated for the dipicrate of structure IV. Compounds similar to structure IV have been prepared (7) from cyclic guanidino acids.

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Contribution from the L. G. Ryan Research Laboratories of Monsanto Canada Limited, Ville LaSalle, Quebec.

TABLE I

1-(β-DIALKYLAMINOETHYL)-IMIDAZOLIDINE-2-THIONES AND THEIR PICRATES

Alkyl group	Yield, %	M.p., °C.	Formula	C		H		N		S	
				Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
CH_3	54.0	94–95	$C_7H_{15}N_3S$	48.53	48.61	8.73	8.63	24.25	24.50	18.50	18.65
		166–167[a]	$C_{13}H_{18}N_6SO_7$	38.81	38.82	4.51	4.51	20.88	20.60	7.97	7.86
C_2H_5	75.7	77–78	$C_9H_{19}N_3S$	53.70	53.97	9.51	9.71	20.88	20.50	15.93	16.10
		141–142[a]	$C_{15}H_{22}N_6SO_7$	41.86	41.94	5.15	5.33	19.53	19.80	7.45	7.75
n-C_3H_7	31.4	74–75	$C_{11}H_{23}N_3S$	57.58	57.31	10.10	9.99	18.32	18.20	13.97	14.15
		124–125[a]	$C_{17}H_{26}N_6SO_7$	44.49	44.59	5.72	5.70	18.33	17.97	6.99	6.83
n-C_4H_9	57.0	43–44	$C_{13}H_{27}N_3S$	60.64	60.64	10.58	10.83	16.33	16.20	12.45	12.40
		115–117[a]	$C_{19}H_{30}N_6SO_7$	46.89	46.81	6.21	6.28	17.28	16.98		

[a]*Picrates.*

TABLE II

POLYAMINES

Compound	Yield,[a] %	Boiling point		n_D	
		°C.	mm. pressure	°C.	Reading
$(CH_3)_2N(CH_2)_2NH_2$[b]	54.5–60.0	104–106	760	25	1.4250
$(CH_3)_2N(CH_2)_2NH(CH_2)_2NH_2$	9.2–17.7	169–180	760	25	1.4583
$(C_2H_5)_2N(CH_2)_2NH_2$[c]	37.5–41.0	78–80	60	25	1.4362
		146–150	760		
$(C_2H_5)_2N(CH_2)_2NH(CH_2)_2NH_2$[d]	17.0–23.2	108–110	19	25	1.4539
		114–116	25		
$(n\text{-}C_3H_7)_2NH(CH_2)_2NH_2$[e]	28.6	96–98	41	23	1.4384
$(n\text{-}C_3H_7)_2NH(CH_2)_2NH(CH_2)_2NH_2$	23.3	154–160	41	23	1.4570
$(n\text{-}C_4H_9)_2NH(CH_2)_2NH_2$[f]	29.4–31.6	114–117	24	26	1.4410
$(n\text{-}C_4H_9)_2NH(CH_2)_2NH(CH_2)_2NH_2$	16.2–17.0	155–164	24	23.5	1.4589
$i\text{-}C_3H_7O(CH_2)_3NH(CH_2)_2NH_2$	8.9	120–124	24	22	1.4465

[a] *The yields reported within ranges represent several runs.*

[b] *Turner (12) reports b.p. 105–108°C.*

[c] *Bloom et al. (3) report b.p. 144–145° at 760 mm.*

[d] *Braz and Skorodumov (4) report b.p. 112–114° at 24 mm., and* n_D^{20} *1.4629.*

[e] *Braz and Skorodumov (4) report b.p. 87–88° at 29 mm., and* n_D^{20} *1.4437.*

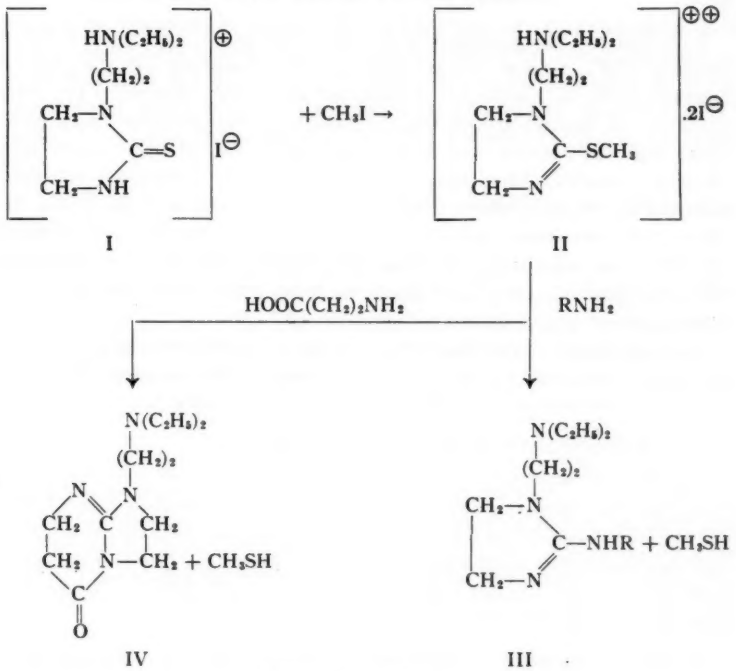
[f] *Braz and Skorodumov (4) report b.p. 107° at 21 mm., and* n_D^{20} *1.4449. Amundsen and Krantz (1) report b.p. 98–101° at 13 mm.*

TABLE III

PICRATES OF POLYAMINES

Compound	M.p., °C. (dec.)	Formula	C		H		N	
			Calc.	Found	Calc.	Found	Calc.	Found
$(CH_3)_2NH(CH_2)_2NH_2$	228–229	$C_{16}H_{19}N_8O_{14}$	35.10	35.36	3.49	3.42	20.51	20.20
$(CH_3)_2NH(CH_2)_2NH(CH_2)_2NH_2$	209–209.5	$C_{24}H_{27}N_{12}O_{21}$	35.18	35.23	3.32	3.41	20.50	20.10
$(C_2H_5)_2NH(CH_2)_2NH_2$[a]	214–215							
$(C_2H_5)_2NH(CH_2)_2NH(CH_2)_2NH_2$[b]	206–207							
$(n\text{-}C_3H_7)_2NH(CH_2)_2NH_2$[c]	192–192.5							
$(n\text{-}C_3H_7)_2NH(CH_2)_2NH(CH_2)_2NH_2$	204–205	$C_{28}H_{35}N_{12}O_{21}$	38.41	38.86	4.03	4.07	19.20	19.50
$(n\text{-}C_4H_9)_2NH(CH_2)_2NH_2$[d]	192–193							
$(n\text{-}C_4H_9)_2NH(CH_2)_2NH(CH_2)_2NH_2$	209–210	$C_{30}H_{39}N_{12}O_{21}$	39.88	40.03	4.35	4.18	18.60	18.59
$i\text{-}C_3H_7O(CH_2)_3NH(CH_2)_2NH_2$	146	$C_{20}H_{26}N_8O_{15}$	38.89	38.93	4.08	4.27	18.13	17.90

[a] *Ristenpart (9) reports m.p. 211°C.*
[b] *Braz and Skorodumov (4) report m.p. 204.5–205.5°C.*
[c] *Braz and Skorodumov (4) report m.p. 192–193.5°C.*
[d] *Braz and Skorodumov (4) report m.p. 187–189°C.*



EXPERIMENTAL[2]

The Addition of Amines to Ethylenimine

The amines described in Table I were prepared by the addition of ethylenimine to the corresponding monoamino derivative by the method of Braz and Skorodumov (4, 5). Their picrates listed in Table II were obtained from their aqueous solutions on addition of saturated aqueous picric acid solution.

In one experiment the primary addition product, N,N-diethyl ethylenediamine (116 gm., 1.0 mole), was refluxed in an absolute ethanol (250 cc.) solution of ethylenimine (21.5 gm., 0.50 mole) in the presence of N,N-diethyl ethylenediamine dihydrochloride (1.4 gm., 0.0075 mole) for 11 hr. After the ethanol was removed by evaporation, the residue was fractionally distilled. In addition to the expected secondary product, N,N-diethyl-N′-(2-aminoethyl) ethylenediamine (b.p. 114–116°C. at 25 mm.; n_D^{25} 1.4539; yield 37.1 gm.; 46.7%), part of the N,N-diethyl ethylenediamine was recovered unchanged. A residue (22 gm.) of higher order addition products also was obtained.

1-(β-Dialkylaminoethyl)-2-imidazolidinethiones

The 1-(β-dialkylaminoethyl)-2-imidazolidinethiones described in Table I were prepared in a similar manner and only the preparation of one of them is given below in detail.

[2]*All melting points are uncorrected. The microanalyses were determined by Micro Tech Laboratories, Skokie, Illinois.*

N,N-Diethyl-N′-(2-aminoethyl) ethylenediamine (109 gm., 0.686 mole) in benzene (250 cc.) was treated with carbon disulphide (58 gm., 0.75 mole) in benzene (100 cc.) under the conditions previously described (7) for the preparation of hexahydropyrimidine-2-thione. The benzene was removed *in vacuo* and the residue was heated at 150°C. for 30 min. under nitrogen at 30 mm. pressure. The residue was extracted with boiling petroleum ether (65–105°C.) (5 × 1 liter). The insoluble residue (16.2 gm.) was discarded. After the petroleum extract was concentrated to 3 liters, crystals (m.p. 74–77°C.) of 1-(β-diethylaminoethyl)-2-imidazolidinethione separated, yield 105 gm. (75.7%). One crystallization from ether (4 cc. per gm.) raised the melting point to a constant value of 77–78°C.

A small sample of the final product was converted into its picrate in aqueous solution in the usual manner. The properties of the picrates of the 1-(β-dialkylaminoethyl)-2-imidazolidinethiones are given in Table I.

1-(γ-Isopropoxypropyl)-2-imidazolidinethione

Crude 1-(γ-isopropoxypropyl)-2-imidazolidinethione was prepared in 70% yield by the method described above for the preparation of the 1-substituted-2-imidazolidinethiones. The product was purified by several crystallizations from ether after which it melted at 56–57°C. The yield of pure product was 36%. Anal. Calc. for $C_9H_{18}N_2OS$: C, 53.44; H, 8.97; N, 13.85; S, 15.85%. Found: C, 53.62; H, 8.84; N, 13.56; S, 16.03%.

1-(β-Diethylaminoethyl)-2-methylmercapto-2-imidazoline Dihydroiodide

Aqueous hydrogen iodide solution (55%) was added dropwise to a solution of 1-(β-diethylaminoethyl)-2-imidazolidinethione (40.26 gm., 0.2 mole) in methanol (100 cc.) at 10–12°C. until a pH of 5.0 was attained. The solution on being cooled to 0°C. gave 40.1 gm. of the hydroiodide salt (m.p. 116–118°C.). Another crop of 20.8 gm. of the hydroiodide salt (m.p. 116–118°C.) was obtained by dilution of the filtrate with ether (100 cc.). The total yield was 92.5%. The melting point was raised to a constant value of 117–118°C. by two crystallizations from absolute ethanol. Anal. Calc. for $C_9H_{20}IN_3S$: C, 32.98; H, 5.93; N, 12.50%. Found: C, 32.82; H, 6.12; N, 12.76%.

A solution of the hydroiodide salt of 1-(β-diethylaminoethyl)-2-imidazolidinethione (58.9 gm., 0.179 mole) and methyl iodide (26.2 gm., 0.185 mole) in methanol (100 cc.) was refluxed for 15 min. After removal of the methanol by evaporation, a crystalline residue (m.p. 120–126°C.) of 1-(β-diethylaminoethyl)-2-methylmercapto-2-imidazoline dihydroiodide was obtained, yield 84.4 gm. (99.8%). Several crystallizations from ethanol raised the melting point to 127–129°C. Anal. Calc. for $C_{10}H_{23}I_2N_3S$: C, 25.49; H, 4.92; N, 8.92%. Found: C, 25.80; H, 5.15; N, 8.62%.

1-(β-Diethylaminoethyl)-2-benzylamino-2-imidazoline Dipicrate

A solution of 1-(β-diethylaminoethyl)-2-methylmercapto-2-imidazoline dihydroiodide (47.1 gm., 0.10 mole) and benzylamine (10.7 gm., 0.10 mole) in methanol (30 cc.) was refluxed for 30 min. After removal of the methanol by evaporation, a semisolid was obtained, yield 42 gm. A portion (2.8 gm.) of

this material was dissolved in water (15 cc.) and saturated aqueous picric acid solution was added. The crude dipicrate (m.p. 170–180°C.) was obtained in 34.8% yield based on the dihydroiodide salt. One crystallization from water raised the melting point to a constant value of 210–211°C. Anal. Calc. for $C_{28}H_{32}N_{10}O_{14}$: C, 45.89; H, 4.41; N, 19.12%. Found: C, 46.09; H, 4.65; N, 18.90%.

Condensation of β-Alanine with 1-(β-Diethylaminoethyl)-2-methylmercapto-2-imidazoline

1-(β-Diethylaminoethyl)-2-methylmercapto-2-imidazoline dihydroiodide (9.4 gm., 0.02 mole) was added to a solution of sodium hydroxide (2.0 gm., 0.05 mole) in water (10 cc.) at 0°C. The solution was extracted with chloroform (3 × 50 cc.) and the chloroform solution was dried over anhydrous sodium sulphate and evaporated. The residue weighed 4.4 gm. (theory 4.3 gm.) and the free base must have been contaminated with some salt.

A portion of the free base (0.80 gm., 0.0037 mole) and β-alanine (0.27 gm., 0.003 mole) were dissolved in absolute methanol (15 cc.) and the solution was refluxed for three hours. During this time methyl mercaptan was evolved. After the methanol was removed by evaporation a gummy product was obtained. The product on treatment with aqueous picric acid solution gave 0.26 gm. (17.34%) of picrate melting at 170–174°C. One crystallization from methanol raised the melting point to 176.5–177°C. Anal. Calc. for $C_{24}H_{28}N_{10}O_{15}$: C, 41.36; H, 4.19; N, 20.08%. Found: C, 41.49; H, 4.18; N, 20.18%.

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RADIOCHEMICAL STUDIES OF GRAPHITE FERRIC CHLORIDE[1]

By R. M. Lazo[2] and J. G. Hooley

ABSTRACT

Graphite ferric chloride, $C_{12}FeCl_3$, was prepared by heating anhydrous ferric chloride with graphite at 305°C. The purified compound containing 53% ferric chloride was not attacked by hot 6 *N* hydrochloric acid and gave an X-ray diffraction pattern which was distinctly different from that of either graphite or ferric chloride. The separation of the graphite layer-planes was increased from 3.36 to 9.4 Å by the intercalation of the ferric chloride molecules.

Tests for exchange between $C_{12}FeCl_3$ and Fe^{+++} ion were made using radioactive Fe^{59}. In no instance was any measurable exchange observed. The compound was subjected to neutron irradiation and the Szilard–Chalmers yield of separable activity calculated and identified. The separated portion contained less than 1% of the total activity and consisted of Fe^{59}, P^{32}, and S^{35}.

The lack of exchange and the low Szilard–Chalmers yield are attributed to the formidable steric hindrance effects which result from the "stacked layer" structure for graphite ferric chloride.

INTRODUCTION

It is known that the layers of carbon atoms in graphite can be intercalated with certain elements and compounds (6). The many examples include such varied materials as potassium (2, 5), bromine (7, 5), ferric chloride (7), and, with accompanying oxidation, bisulphate ion (8). In many of these cases a distinction is made between the "lamellar" compound initially formed and the "residue" compound formed from it by heat or solvent action (3). X-ray studies show that in the lamellar complex the layers of carbon atoms are about 8 Å apart as compared with 3.34 Å for graphite, whereas in the residue compounds the separation returns to 3.34 Å. The residual adduct in the latter case is believed to be very strongly held on lattice imperfections (4).

In the case of ferric chloride between 60 and 72% enters the lattice in the range 200 to 309°C. Treatment of these products with acid reduces the amount to 53%, which corresponds closely to $C_{12}FeCl_3$ and leaves a layer separation of 9.4 Å. The residue compound, containing 5% $FeCl_3$, is obtained above 410°C. In the lamellar compound with 53% chloride it is believed that the carbon is bonded to adjacent layers of chlorine atoms, which in turn enclose a layer of iron atoms. Rudorff (7) suggests that there is a polarization of the conductivity electrons of the carbon layers toward the central layer of iron atoms, but that these remain essentially ionic. There will then be electrovalent bonding of the chloride ions to the macro positive ion layer planes. The original purpose of this work was to learn something about these bonds by measuring the exchange of iron between the compound and iron in solution and by measuring the extent of any Szilard–Chalmers reaction on neutron irradiation. The complete lack of exchange, however, means that other methods must be used at least within the time and temperature limits of this work.

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Contribution from the Department of Chemistry, University of British Columbia, Vancouver, B.C., with financial assistance from the National Research Council of Canada.
[2]*Holder of an N.R.C. Summer Scholarship 1950. Present address: Bell Telephone, Murray Hill, New Jersey, U.S.A.*

EXPERIMENTAL

1. *Preparation of Materials*

(*a*) *Ferric Chloride Anhydrous*

Dry chlorine was passed over c.p. iron powder at 350°C. in a glass tube until no more hexagonal platelets of a deep red wine color formed in the cool portion of the tube. The crystals were cooled in a stream of dry air and removed and handled only in a dry box. The active chloride was prepared by using radioactive iron wire with the powder.

(*b*) *Graphite Ferric Chloride, $C_{12}FeCl_3$*

Acid purified, 200-mesh graphite (G66 of Fisher Scientific Co.) was mixed with three times its weight of anhydrous ferric chloride, sealed in a Carius bomb tube, and heated for 12 hr. at 305°C. The excess ferric chloride was removed by three successive 12 hr. refluxings with boiling 6 *N* HCl.

2. *Analysis of the Graphite Ferric Chloride*

(*a*) *Acid-soluble Ferric Chloride*

Five grams of purified product were further refluxed with acid for six hours. The extract, evaporated to 1/10 of its volume, gave no color with ammonium thiocyanate solution. From the known sensitivity of this test, there must have been less than 10 μgm. of ferric ion extracted per gm. of graphite ferric chloride.

A second test was made on purified $C_{12}FeCl_3$ containing 2.3×10^5 counts of Fe^{59} per min. per gm. The extract prepared as above and counted showed less than 4 μgm. of ferric ion extracted per gm. of $C_{12}FeCl_3$.

(*b*) *Gravimetric Analysis*

From the original weight of graphite and the final weight of purified compound for eight preparations, a figure of $53.04 \pm 0.09\%$ $FeCl_3$ was obtained. This gives a ratio of $FeCl_3$ to C of 1 to 11.96 ± 0.03.

(*c*) *X-ray Analysis*

These measurements were made on both graphite and $C_{12}FeCl_3$ with a Phillips Geiger-Counter X-ray Spectrometer using the 1.539 Å Cu line. Fig. 1 is a plot of intensity against glancing angle, which is θ in the equation $n\lambda = 2d \sin\theta$. Table I lists the values for graphite ferric chloride. The first

TABLE I

THE PRINCIPAL DIFFRACTION LINES OF GRAPHITE FERRIC CHLORIDE POWDER

2θ, degrees	d, Å	I/I_{max}
8.1	10.90	0.30
9.4	9.40	0.64
11.8	7.49	0.25
19.0	4.66	1.00
26.8	3.32	0.21
28.5	3.13	0.81
52.2	1.42	0.11
58.8	1.57	0.10
68.1	1.37	0.12

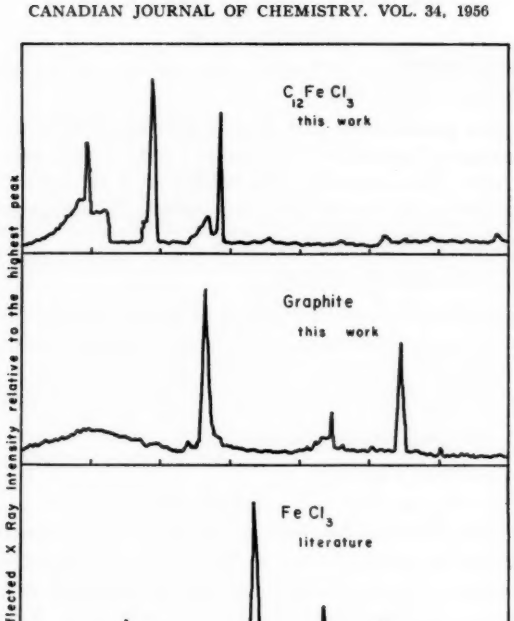

FIG. 1. The reflection of X rays from a powder.

peak for this compound gives a value of $d = 9.40$ Å and is interpreted as the distance between carbon layers. The first peak for graphite at 13.2° corresponds to the layer-plane separation of 3.36 Å. The literature values are 9.4 Å for $C_{12}FeCl_3$ (7) and 3.41 Å for graphite (1). For comparison the plot for $FeCl_3$ as taken from the literature (1) is included.

3. Preparation and Measurement of Radioactive Iron

Pure iron wire was activated in the Canadian Atomic Energy Project reactor. A mixture of 47 day Fe^{59} emitting beta and gamma rays and four year Fe^{55} emitting weak X rays was received with an activity of 0.06 mc. of Fe^{59} per gm. and 0.3 mc. of Fe^{55} per gm. The decay curve over a five-month period was linear with a half life of 47 days. This shows that the weak X rays from Fe^{55} were not detected and that for correction of activities to zero time, a half life of 47 days can be used.

Measurements were made with a self quenching counter with a 3 mgm. per cm.^{2} window and a 150 volt plateau. It was shielded to a background count of 42 per minute. The pulses were counted by a Nuclear Instrument Company Model 163 scaling unit.

The solid graphite ferric chloride samples were always less than 0.2 mgm. cm.$^{-2}$ and were therefore not corrected for self absorption. Uniform samples

of this thickness were prepared as follows: About 20 mgm. of finely divided powder was accurately weighed and slurried with water. This was slowly added to a Buchner funnel full of water and containing a 6 cm. diameter filter paper under slight suction. After the water had run through, four or five circles of damp, sample covered paper were cut at random with a 1.6 cm. diameter cork borer. These were dried in a desiccator and then counted. The over-all spread was never over 5% and the average count was used.

The activities of the evaporated ferric chloride solutions were corrected for self absorption by extrapolating the activities per unit volume of aliquots of 0.2, 0.4, 0.6, and 0.8 ml. to zero volume.

EXCHANGE OF IRON BETWEEN $C_{12}FeCl_3$ AND FERRIC CHLORIDE

An 0.01 to 0.15 gm. sample of $C_{12}FeCl_3$ was mechanically shaken with 5 ml. of 0.05 to 0.50 *M* $FeCl_3$ solution and centrifuged. The specific activities of the washed solid and of the solution were determined. These were corrected for background, decay, and, in the case of the evaporated solution, for self absorption.

In the first set of experiments the graphite ferric chloride had an activity of 1255 ± 10 c.p.m. per mgm. of iron. For times up to four months at 20°C. and a pH of 5 this activity remained the same and the solution acquired none. The same result was obtained in eight hours at 80°C. and in five other solvents. These were acetone, diethyl ether, isopropyl ether, ethanol, and benzyl alcohol at 20°C. for four days and the latter two at 50° and 190° respectively for four hours.

In the second set, the activity was in water solution to the extent of 580 c.p.m. per mgm. of iron. For times up to four months at 20°C. and a pH of 1.0 none of this was transferred to the solid.

THE SZILARD–CHALMERS REACTION IN GRAPHITE FERRIC CHLORIDE

A 1.50 gm. sample of purified $C_{12}FeCl_3$ was irradiated for 48 hr. in a neutron flux of 4×10^{12} per cm.^{2} per sec. in the Canadian Atomic Energy Project reactor at Chalk River, Ontario. The acid extract was separated into its components and the activities of these and that of the solid were studied by measuring the absorption characteristics of their radiations.

1. Separation of the Components

The known products of the irradiation are listed in Table II along with the calculated activity of each component. The amounts of Cl^{36} and Cl^{38} are negligible and the Fe^{55} radiation is not detected by our counter. This leaves only Fe^{59}, S^{35}, and P^{32} as measurable components. These were separated in the extract according to the following method which is similar to one used by Wilk (9).

An 0.100 gm. sample of irradiated $C_{12}FeCl_3$ was refluxed with 200 ml. of 6 *N* hydrochloric acid for six hours and centrifuged. To the aqueous layer was added a few drops of 30% hydrogen peroxide to ensure oxidation to ferric ion. The colorless solution was then shaken with successive quarter volumes of

TABLE II

THE 48 HR. IRRADIATION OF 1.5 GM. OF GRAPHITE FERRIC CHLORIDE IN A NEUTRON FLUX OF 3.5×10^{12} CM.$^{-2}$ SEC.$^{-1}$

Isotope	Half life	Radiation in Mev.	Range in mgm. cm.$^{-2}$	Calculated activity in mc./gm. of compound 12 hr. after activation
Fe^{55}	3.0 yr.	γ 0.07		0.02
Fe^{59}	45.5 days	β 0.26, 0.46 γ 1.10, 1.30	70, 150	0.005
P^{32}	14.30 days	β 1.7	770	0.01
S^{35}	87.1 days	β 0.17	30	1.3
Cl^{36}	4×10^5 yr.	β 0.66	250	0.0002
Cl^{38}	38 min.	β and γ		10^{-4}

diethyl ether saturated with hydrochloric acid, and finally washed with an equal volume of the solvent. The ether extracts were combined and stripped with distilled water. The activities of the resultant solutions were measured and the components differentiated by absorption measurements to show that the activities present corresponded to those shown in Table II.

Figs. 2 and 3 give these absorption curves and show that most of the

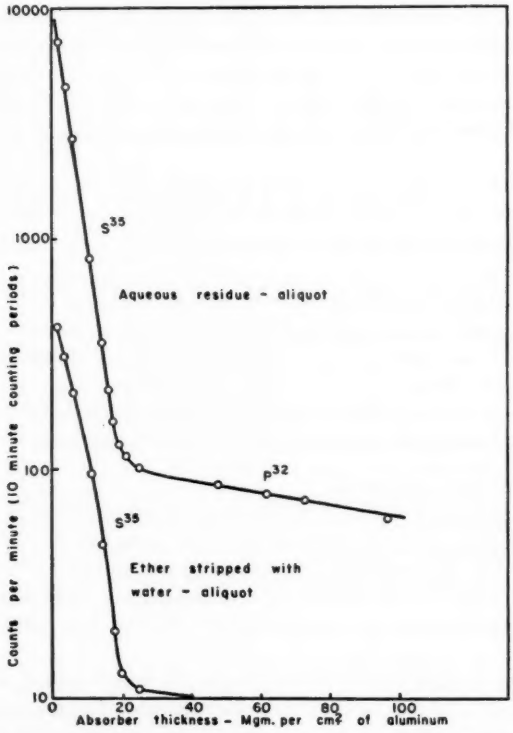

FIG. 2. The absorption characteristics of the separated S^{35} and P^{32}.

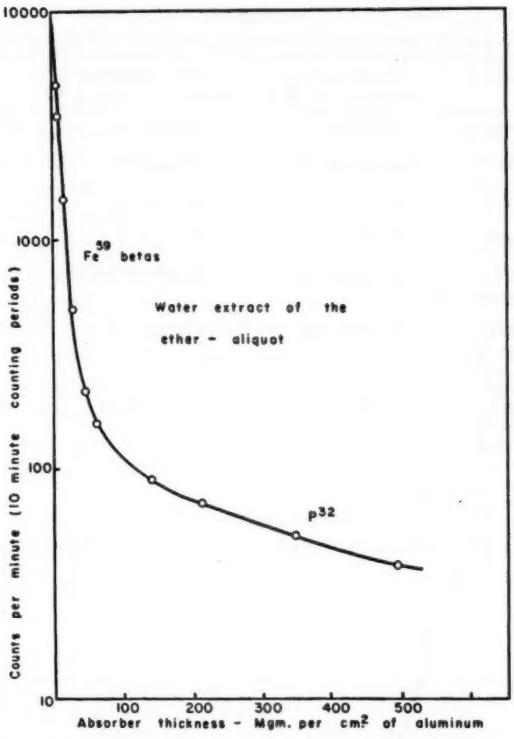

FIG. 3. The absorption characteristics of the separated Fe^{59} and P^{32}.

S^{35} and P^{32} remained in the original aqueous acid extract and that all the iron was transferred to the ether layer and from there to the water extract of that layer.

2. Total Activities of the Original Extract and the Solid

The conditions of time and temperature of extraction were varied and in three extractions the solid was ground with the acid. The results are presented in Table III. They show that 6 *N* hydrochloric acid extracts $0.683 \pm 0.010\%$ of the total activity, whether at 80° or 100°C. and whether for 15 min. or 16 hr. They also show that grinding the solid raises this value to $0.730 \pm 0.007\%$.

The absorption characteristics of the radiations were measured and are shown in Fig. 4. They are the same for the extracted solid and for the acid extract. Both of these, however, show less weak components than does the irradiated compound before extraction. Perhaps the latter process volatilized some of the weakest component, S^{35}. In any case, the over-all process removed the same percentage of each of the three radioactive components.

TABLE III

THE ACID EXTRACTION OF IRRADIATED GRAPHITE FERRIC CHLORIDE

Conditions	Initial activity in c.p.m. $\times 10^{-5}$	Total separated activity in c.p.m. $\times 10^{-3}$	% extracted
1. 4 *N* HCl at 80°C. stirred 15 min.	58.11±0.11	39.6±1.9	0.681±0.033
2. 6 *N* HCl at 100°C. refluxed 4 hr.	134.32±0.26	92.4±1.7	0.688±0.013
3. 6 *N* HCl at 100°C. refluxed 8 hr.	120.0±0.23	82.0±1.6	0.683±0.013
4. 6 *N* HCl at 100°C. refluxed 16 hr.	87.06±0.16	59.4±1.2	0.682±0.014
5. 6 *N* HCl at 25°C. ground in a mortar for 1 hr.	38.56±0.10	28.08±0.16	0.728±0.004
6. 6 *N* HCl at 100°C. ground between two ground-glass plates before extraction	11.99±0.03	8.7±0.17	0.726±0.014
7. 6 *N* HCl at 100°C. as in "6" but with fine Al_2O_3 grinding powder	13.187±0.04	9.72±0.19	0.737±0.015
Average for non-ground samples 1 to 4			0.683±0.010
Average for ground samples 5 to 7			0.730±0.007

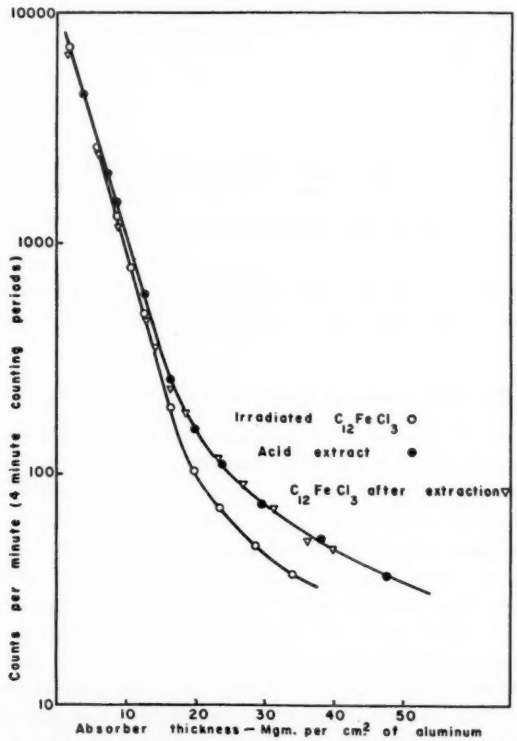

FIG. 4. The absorption characteristics of the irradiated $C_{12}FeCl_3$.

DISCUSSION

The extraction of activity from neutron irradiated $C_{12}FeCl_3$ could be explained by the initial presence of free ferric chloride. It has been shown, however, that the purified compound contains less than 4 μgm. of Fe per gm. as free chloride. This could account for only 0.3% of the separated activity. The ferric chloride must therefore be bonded to the graphite and bonded in such a fashion as to prevent exchange of iron with a surrounding solution under the attained conditions. Activation of an iron atom with neutrons, however, breaks the bond. The fact that only 1% of the total iron atoms so activated was extractable shows that the remaining 99% recombined with the lattice on dissipation of the energy or/and was not in a position to be reached by the acid. The latter is probably true for the sulphur and phosphorus produced from the chlorine because no stable way of fitting them into the lattice is known, and yet only 1% of them was extracted by acid. It is therefore assumed that the extracted activities came only from the surface layers of the crystal. Grinding would expose fresh surfaces and thereby increase the per cent of extractable activity just as was observed.

ACKNOWLEDGMENT

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ATTEMPTED DELIGNIFICATIONS WITH SODIUM BICARBONATE - CARBON DIOXIDE, AND WITH ANHYDROUS LIQUID AMMONIA, UNDER PRESSURE[1]

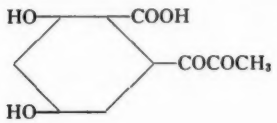
By M. M. Yan[2] and C. B. Purves

ABSTRACT

Finely divided spruce wood was heated with aqueous sodium bicarbonate and excess carbon dioxide up to 160° and about 400 p.s.i. in attempts to carboxylate the lignin according to the Kolbe–Schmitt method and to extract the product as a soluble sodium salt. Only small amounts of lignin were removed, together with larger amounts of the holocellulose. Heating the wood with anhydrous liquid ammonia up to 100° and about 900 p.s.i. extracted only small amounts of material from the softwood spruce, but 25 to 30% of the lignin was removed from the hard woods beech, birch, and maple and 52% from rye straw. The solution of ammonium chloride or sodium cyanide in the liquid ammonia increased these percentages substantially, and also the concomitant extraction of holocellulose.

INTRODUCTION

In an interesting article published in 1943, Kulka and Hibbert (15) pointed out that the oxygenated phenyl propane derivatives resulting from the ethanolysis of wood lignins bore some similarity to the compounds I and II isolated by Oxford and Raistrick (16) from certain strains of *Penicillium brevi-compactum* grown on glucose. The similarity was close in the side chains,



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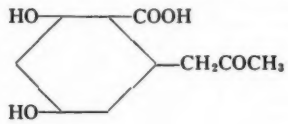

II

but the products from lignin differed in being based on vanillin and syringyl units, which were phenolic methyl ethers as well as free phenols, and also in having no carboxylic acid groups. The latter difference was attributed by Kulka and Hibbert to the carboxylation of the non-acidic precursors of I and II by a biochemical process analogous to the well-known Kolbe–Schmitt reaction, in which a phenol was carboxylated by carbon dioxide. In a typical Kolbe–Schmitt synthesis, a mixture of the phenol with anhydrous sodium or potassium carbonate, or the dry sodium or potassium phenolate, was treated at an elevated temperature with carbon dioxide under pressure (6). The carboxyl group entered ortho, or more rarely, para, to the phenolic hydroxyl group, and the yields were generally good. The synthesis, however, proceeded

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with remarkable ease with polyhydric phenols; phloroglucinol when dissolved in glycerol with potassium bicarbonate was carboxylated to a considerable degree even at room temperature (4), and resorcinol required to be warmed with aqueous potassium bicarbonate for only a short time (2). Although lignin *in situ* contained few, if any, free phenolic groups, they were known to be produced in several reactions such as ethanolysis. If this occurred in the conditions of the Kolbe–Schmitt synthesis, the lignin might also acquire carboxyl groups, and be removed from the wood as a water-soluble sodium salt. The present research was designed to explore this possibility.

Approximately equal weights of solvent-extracted spruce wood meal, solid sodium bicarbonate, and solid carbon dioxide were sealed with 20 parts of distilled water in a suitable autoclave, which was then heated for 20–24 hr. as described in Table I. The yield of the residual, undissolved meal and its

TABLE I

KOLBE–SCHMITT COOKS WITH SPRUCE WOOD MEAL[a]

Cook No.	Ratio to wt. of wood[b]		Conditions			Wood residue		Extracted	
	CO_2	$NaHCO_3$	°C.	Hr.	P.s.i.	Yield, %	Lignin,[c] %	Lignin,[d] %	Holocellulose,[e] %
1	1.0	1.0	100	20	265	~100	26.5	—	—
2	0.7	1.0	158	24	215	83.4	29.1	−0.6	<17
3	1.0	1.0	163	24	400	76.7	26.2	2.3	21
4	0	0	163	24	0	75.5	30.9	−2.4	<25
5	0	0	159	24	0	75.1	31.4	−2.9	<25

[a] *Klason lignin, 28.5; methoxyl, 4.7%. All percentages based on original oven-dry wood.*
[b] *To one part of wood and 20 parts of water.*
[c] *Analytical figures multiplied by yield %/100.*
[d] *Data in preceding column subtracted from 28.5% (footnote "a").*
[e] *Calc. as 100 minus (residual yield and extracted lignin).*

Klason lignin content made it possible to calculate the approximate percentage of the original wood that had been extracted as lignin, and, by difference, the amount extracted as non-lignin or holocellulose. The first cook (experiment 1) showed that very little material was removed at 100°. At 158–163°, the extraction of lignin was also negligible, and sometimes small negative values suggested that Klason lignin had been manufactured from other substances in the wood (cook 2). Corey, Calhoun, and Maass (8) found that the apparent Klason lignin content of spruce wood heated in water buffered to pH 3 for 96 hr. at 140° increased from 26.3% to 28.6%, and Aronovsky (1) made a similar observation with pine (another softwood) heated in water at 170°. These observations were confirmed in cooks 4 and 5, in which water alone was used. The low extraction of Klason lignin in the Kolbe–Schmitt cooks and the high extraction of holocellulose (right hand column) made it probable that the sodium bicarbonate–carbon dioxide system served only as a buffer which slightly reduced the hydrolytic action of water (14) on the wood polysaccharides.

Since the failure of the Kolbe reaction in the above experiments might have originated in a lack of free phenolic hydroxyl groups in the lignin, later trials were carried out on wood samples that had been pretreated with acids or alkalis. The conditions of these pretreatments (Table II) were expected to

TABLE II

KOLBE COOKS WITH PRETREATED SPRUCE MEAL[a]

Cook No.	Pretreatment			Kolbe cooks[b]	Wood residue		Extracted	
	Medium	Hr.	°C.		Yield, %	Lignin,[c] %	Lignin,[d] %	Holocellulose,[e] %
6	H_2O	24	162		75.3	31.2	−2.7	<25
				Cook[f]	72.9	30.0	−1.5	<27
7	0.5% HCl	4	130		67.8	25.2	3.3	29
				Cook	52.6	25.6	2.9	45
8	0.5% HCl	2	100		81.6	26.9	1.6	17
				Cook	59.8	25.6	2.9	37
9	0.5% HCl	2	100		80.0	26.8	1.7	18
				Cook	63.8	27.0	1.5	35
10	1% NaOH	3	100		84.9	26.3	2.2	13
				Cook	74.9	24.6	3.9	21
11	Meal–NaOH[g] (dried)	—	—	Cook[g]	68.4	24.4	5.0	27

[a]*Klason lignin, 28.5%. All percentages based on weight of original oven-dry wood.*
[b]*Water: wood: CO_2: $NaHCO_3$ = 20: 1: 1: 1 by weight; cooks at 158–160° for 24 hr. at about 400 p.s.i.*
[c]*Analytical figures multiplied by yield %/100.*
[d]*Data in preceding column subtracted from 28.5% (footnote "a").*
[e]*Calc. as 100 minus (residual yield and extracted lignin).*
[f]*At 100°.*
[g]*One part NaOH and two parts wood meal dried over P_2O_5 near 20°. Klason lignin 29.4%. Cooked in CO_2 at 400 p.s.i. for 65 hr.*

liberate more free phenolic groups in the lignin by hydrolysis or saponification, but neither the pretreatments nor the subsequent Kolbe–Schmitt cooks removed substantial quantities of the lignin. Cook 6 showed that the process at 100° had a negligible effect on wood pretreated in water at 162°, just as it had on the original wood (Table I, cook 1). The Kolbe–Schmitt cook, however, did extract a substantial additional amount of holocellulose from the samples prehydrolyzed with boiling aqueous acid, perhaps because of the superior solvent action of a slightly alkaline system on partly degraded hemicelluloses (Table II, cooks 7–9). The same effect was noticeable to a lesser degree when the pretreatment was with boiling alkali (cook 10). Since the Kolbe–Schmitt reaction often proceeded better when carried out in the absence of water, the last experiment involved the action of carbon dioxide under pressure on wood meal which had been impregnated with sodium hydroxide and dried to constant weight. A subsequent extraction with warm water removed little lignin, but much of the holocellulose.

The possibility existed that the carbohydrate content of the wood was

interfering in some way with the response of the lignin to the carboxylating agent. An isolated spruce periodate lignin (17) was accordingly cooked with aqueous sodium bicarbonate – carbon dioxide at 160° and near 400 p.s.i. for 24 hr., but only 22% went into solution. Isolated maple ethanol lignin (3) dissolved to the extent of only 10% in a similar cook at 100°, whereas 13.4% became soluble when a sample was boiled in water for 24 hr. In both cases the light-colored, powdery, ethanol lignin was changed to a very dark, hard, coal-like state. These experiments made it clear that the failure of the Kolbe–Schmitt reaction to remove substantial quantities of lignin could not be attributed to the presence of the wood polysaccharides, but was inherent in the lignin itself. It was probable that resinification caused by the temperature and alkalinity (5) kept the bulk of the lignin insoluble and any carboxylation that occurred had a negligible effect in promoting solubility.

The decision to investigate the action of anhydrous liquid ammonia on woods was based on the facts that it was neither an acidic nor an alkaline reagent, was a much better solvent than water for many organic substances, and differed from water in its capacity to penetrate and swell the crystalline as well as the amorphous portions of cellulose (9). These properties suggested that anhydrous liquid ammonia under pressure might extract much of the lignin and hemicellulose from woods with little chemical change beyond the ammonolysis of any ester linkages present. Freudenberg and his collaborators (11, 12) studied the action on several lignins and woods of solutions of alkali metals and amides in liquid ammonia. An isolated spruce lignin, when treated for 24 hr. at 20° in this way with potassium or potassium amide, was rendered completely soluble in the strongly alkaline solution produced by removing the ammonia and adding water; in similar circumstances 50% of spruce wood meal dissolved, and the soluble portion included two-thirds of the lignin. Later investigations of the same type were described in a series of articles by Shorygina and co-workers (18). Extensive chemical change, including demethylation of the lignin, was involved in these reactions, doubtless because in liquid ammonia an alkali metal would function as one of the strongest reducing agents known, and an alkali metal amide would be a strong base (10).

In the present work, the weight ratio of anhydrous liquid ammonia to the oven-dry weight of the wood meal was 15 : 1, but the meal was added in an air-dry condition containing about 7% of moisture. The concentration of water in the system was thereby increased from about 0.03% to about 0.5%. Control experiments made with maple wood and rye straw meals which had been thoroughly dried over phosphorus pentoxide showed, however, that such drying increased the amount extracted by less than 1%. Special care was taken to eliminate the access of adventitious moisture while the ammonia was removed at the end of the extraction. The yield of undissolved wood and its Klason lignin content furnished the approximate amounts of holocellulose and lignin extracted. Unlike the results of the Kolbe–Schmitt cooks, the latter amounts were never negative.

As the data of Table III show, anhydrous liquid ammonia extracted only 9% of the Klason lignin from spruce wood even at 100°, or at a temperature

TABLE III

EXTRACTION OF WOODS AND STRAW WITH LIQUID AMMONIA[a]

Expt. No.	Conditions[b]		Residual meal		Extracted		Per cent of lignin extracted
	°C.	Hr.	Yield, %	Lignin, %	Lignin, %	Holocellulose, %	
Spruce with 28.5% lignin							
1	25	16	97.0	—	←3→		—
2	45	44	—	28.4	—	—	—
3	100	65	96.8	25.9	2.6	0.6	9
Birch with 19.2% lignin							
4	75	40	88.0	15.2	4.0	8.0	21
5	100	3	91.7	16.3	2.9	5.4	15
6	100	65	85.7	12.8[c]	5.5	8.8	30
Beech with 22.7% lignin							
7	75	40	90.7	18.7	4.0	5.3	18
8	100	24	89.5	17.2	5.5	5.0	24
Maple with 21.4% lignin							
9	75	40	89.6	16.8	4.6	5.8	22
10	100	24	88.4	16.1	5.3	6.3	25
Rye straw with 19.7% lignin[d]							
11	100	65	80.1	9.7	10.0	9.9	51
12[e]	100	24	76.5	9.5	10.2	13.3	52
13[e]	100	3	81.6	9.5	10.2	8.2	52
14[e]	25	65	88.6	13.3	6.4	5.0	33

[a]*Air-dry samples. Calculations as in footnotes to Tables I and II.*
[b]*Ratio of liquid NH_3 to bone-dry sample, 15: 1 by weight.*
[c]*Original birch had 18.3% lignin.*
[d]*Data corrected for ash in straw (6.46%) and in Klason lignin.*
[e]*Total moisture in system less than 0.1%.*

fairly close to the critical temperature of 133° recorded for this solvent. Extraction of birch, beech, and maple samples at 100° for 24 to 65 hr., however, removed 24 to 30% of all the lignin present, and the amount increased to just over 50% with the rye straw. The low response of the softwood, spruce, as compared to those of the three hardwoods, was in agreement with the general behavior of the two classes of wood toward other methods of extraction (14), and the still greater response of the rye straw was also to be expected. Comparison of experiments 1 and 3; 7 and 8, and 9 and 10; and 13 and 14 showed that an increase in temperature produced an insignificant change in the amount of material extracted by the liquid ammonia from spruce, a moderate increase in the amounts from the hardwoods, and a major increase in the amount from the rye straw.

In all the experiments described in Table III, the ammonia cellulose, if produced in wood as in cellulose itself, would be of type I (9). A type II ammonia cellulose with a greatly expanded unit cell was known to exist below −30°, and Clark and Parker (7) found that in these conditions cellulose fibers were swollen to three times their original diameters. It seemed desirable to carry out some extractions at less than this temperature. Air-dry spruce and rye straw meals were accordingly extracted with anhydrous liquid ammonia at its boiling point of −33° for 200 hr., but the losses in weight were negligible,

even in the case of the straw. Black spruce chips, however, increased in volume by only 6% when soaked in liquid ammonia at −33° for 22 hr., and it was concluded that the presence of the lignin prevented much swelling of the cellulose. These swollen chips contracted to slightly less than their original volume when the ammonia was allowed to evaporate in the air. Similar but more detailed experiments were made on other woods by Stamm (19), who also noted that the amounts extracted by liquid ammonia near −33°, and by hot water, were about the same.

Although anhydrous liquid ammonia by itself had only a limited extractive action on lignin *in situ*, it seemed possible that solutions of certain salts might be more effective, since in the ammonia system salts like ammonium chloride were known to be ionized and to function as acids (10). Table IV summarizes

TABLE IV

EXTRACTIONS WITH VARIOUS SALTS IN LIQUID AMMONIA[a]

Expt. No.	Salt[b]	Residual meal		Extracted		Per cent of lignin extracted
		Yield, %	Lignin, %	Lignin, %	Holocellulose, %	
Spruce with 28.5% lignin						
15	NH_4Cl	88.0	24.6	3.9	8.1	14
16	NH_4Cl	87.3	23.9	4.6	8.1	16
17	$(NH_4)_2SO_3$	97.0	25.7	2.8	0.2	10
18	$(NH_4)_2SO_4$	96.4	27.0	1.5	2.1	5
19	NaCN[c]	75.3	23.6	4.9	19.8	17
Birch with 18.3% lignin						
20	NH_4Cl	77.3	11.1	7.2	15.5	39
21	$(NH_4)_2SO_3$	79.6	11.5	6.8	13.6	37
Rye straw with 19.7% lignin[d]						
22	NH_4Cl	79.1	8.2	11.5	9.4	58

[a] *Meal samples air-dry. Calculations as in footnotes to Tables I and II.*
[b] *Ratio of liquid ammonia to bone-dry sample to salt, 15 : 1 : 0.75 by weight. All mixtures heated at 100° for 65 hr.*
[c] *Ratio of liquid ammonia to bone-dry sample to salt, 15: 1: 4.5 by weight.*
[d] *Data corrected for ash in straw (6.46%) and in Klason lignin.*

some relevant experiments, made at 100° for 65 hr. with 4.5% solutions. Of the added ammonium salts, the chloride had the most pronounced action, and raised the amount of lignin extracted from 9% to about 15% in the case of spruce (Table III, expt. 3, and Table IV, expts. 15, 16), from 30% to 39% for birch, and from about 50% to 58% for the rye straw. The extraction of holocellulose from the two woods, but not from the straw, was also substantially increased. Ammonium sulphite in liquid ammonia, which was considered to be the nearest equivalent to the sulphite cook in the aqueous system, was of negligible advantage for spruce, but was almost as good as was ammonium chloride for birch (Table IV, expts. 17 and 21). The extraction of 37% of the lignin probably did not involve sulphonation, because no sulphonic acid groups could be detected in the birch wood residue by the color test employing *p,p'*-azodimethylaniline in acetic acid (13). The addition of ammonium sulphate was of no value (expt. 18), but this salt, like the sulphite, was reported

to be almost insoluble in liquid ammonia. Since sodium cyanide was very soluble, it was possible to use a 23%, instead of a 4.5%, solution, and no less than 17% of the lignin in spruce wood was extracted (expt. 19). Sodium cyanide was presumably non-acidic in liquid ammonia, and its pronounced solvent action on both the lignin and the hemicellulose was unexpected.

Although only minor portions of the wood lignins had been extracted in the experiments just described, the liquid ammonia might have promoted physical or chemical changes which rendered the residual lignin extractable by other reagents. To test this possibility, the spruce and birch wood residues from extractions using liquid ammonia alone, and ammonia containing ammonium chloride or sulphite, were boiled for two hours with 1% aqueous sodium hydroxide. The additional amount of lignin extracted ranged from 2.2% to 8.7% of that in the original wood, but this small loss was usually accompanied by a much greater additional loss of holocellulose.

EXPERIMENTAL

Materials and Analytical Methods

All the wood meals and the rye straw were exhaustively extracted first with alcohol–benzene, then with alcohol, and finally with hot water. After being dried in the air, the meals were used in mesh sizes 20–100 for the rye straw, 40–100 for the spruce, and 60–80 for the beech, birch, and maple samples. The commercial liquid ammonia was claimed to be of 99.95% purity and to contain only 0.03% of water.

Klason lignin determinations were carried out in duplicate on 0.1 gm. to 0.6 gm. samples by scaling down the standard T.A.P.P.I. method (20); all results were corrected for moisture content, and also for ash when the latter was considerable, as it was for the rye straw.

Cooks with Sodium Bicarbonate – Carbon Dioxide (Tables I and II)

A stainless steel bomb of 130 cc. capacity and with walls 12 mm. thick was fitted with a stout, stainless steel lid with a lead gasket. Closure was effected by a bolt which pressed against the top of the lid. The other end of the bolt was anchored into a heavy cap, the inner part of which engaged a screw threaded on the outside of the bomb.

The bomb was loaded with 90 cc. of distilled water, 4.5 gm. of sodium bicarbonate, and an equal weight of the air-dry wood meal. Carbon dioxide was bubbled through the solution to remove air, 4.5 gm. of solid carbon dioxide was quickly added, and the bomb sealed. This weight of carbon dioxide gave a pressure of about 400 p.s.i. at 160°. The bomb was heated either in a steam bath at 100°, or in a thermostatically controlled oil bath, for the prescribed time and was then cooled in water. After the pressure had been carefully released the wood meal was removed, thoroughly washed with water, and dried in the air.

Prior to being cooked, some wood samples, 7.5 gm., were extracted by 150 cc. of aqueous acid or alkali (Table II). Hydrolyses at 100° were carried out under reflux at atmospheric pressure, but a stainless steel bomb of 280 cc. capacity (see below) was used when the temperature was higher. One wood sample was

soaked in 17.5% aqueous sodium hydroxide for one hour at room temperature in a nitrogen atmosphere. After being recovered by filtration and pressing, the meal was dried for several weeks *in vacuo* over phosphorus pentoxide. The dry, yellow product contained 29.4% of Klason lignin, after correction for 33% of sodium hydroxide.

Cooks with Anhydrous Liquid Ammonia (Tables III and IV)

The vapor pressure of liquid ammonia at 100° was about 910 p.s.i. and it was necessary to employ the thick-walled bomb just described. The lid was replaced with a rubber stopper through which a glass inlet tube just passed, and through which a glass exit tube projected. This projection ended just above a level in the bomb corresponding to a volume of 70 cc., equivalent to 50 gm. of ammonia at −60°. After being weighed, the assembly was thoroughly chilled to about −60° in a bath of acetone containing solid carbon dioxide, and liquid ammonia was added from a cylinder until liquid was seen in the exit tube. The assembly was then disconnected and quickly reweighed to make sure that 50±1 gm. of liquid ammonia had actually been added.

A weight of air-dry wood corresponding to 3.33 gm. oven-dried, plus 2.5 gm. of the particular salt present in some experiments, was chilled to −60° in a wide-mouthed weighing bottle and was quickly added to the liquid ammonia in the bomb. If this chilling was inadequate, a violent evolution of ammonia gas scattered the meal. The bomb was then securely sealed with its lid and screw cap before atmospheric moisture had a chance to freeze on the threaded surface. Not more than 20 min. was required for the entire filling operation. When the oil bath was used to heat the bomb, care was taken to keep oil away from the threaded portion, and, when steam was used, all moisture had to be removed from this portion by subsequent heating for 30 min. in an air bath at 100°. Neglect of this precaution made it very difficult to open the bomb after it had been thoroughly chilled, first to −15°, and then to −60°, because ice had formed in the threads.

The open bomb, still kept at −60°, was quickly closed with a rubber stopper carrying an inlet tube for dry nitrogen gas or liquid ammonia, an exit tube for gaseous ammonia terminating just below the stopper, and another exit tube for wood meal and liquid ammonia terminating just above the bottom of the bomb. The two exit tubes, each with a stopcock of bore large enough to create no obstruction, led through a rubber stopper into a sintered glass filter crucible. This stopper was also pierced by a safety tube whose outer end was protected from atmospheric moisture by a guard tube containing pellets of sodium hydroxide. A Buchner suction filter flask received the effluent from the crucible. This assembly permitted the contents of the bomb to be transferred to the filter near −60°, and the wood meal to be washed about six times with fresh liquid ammonia, all without access of air or moisture. When the washing was complete, the bomb was allowed to attain room temperature, a stream of nitrogen meanwhile being maintained to assist in the evaporation of the ammonia. Any of the dry wood meal remaining in the bomb was then transferred to the filter and the last traces of ammonia were removed by passing dry air through the assembly for 12 hr. When a salt had been added to the cook, the

ammonia-free wood meal was thoroughly extracted with warm water and was again air-dried.

In several experiments, the liquid ammonia filtrate was evaporated (with exclusion of moisture) to a light brown, transparent, brittle resin which was dried to constant weight over phosphorus pentoxide. Since this weight was usually very slightly higher than the loss in weight the wood meal incurred in the cook, it seemed probable that the products included combined ammonia. Crystals of acetamide, indeed, occasionally separated from the extract.

A second stainless steel bomb, of lighter construction and of 280 cc. capacity, was sometimes used in liquid ammonia cooks at 45° or less. The lid of this bomb was provided with a $\frac{1}{8}$ in. needle valve for introducing the ammonia, and with an ammonia pressure gauge reading up to 300 p.s.i. This bomb was also used to carry out cooks at $-33°$ and atmospheric pressure for long times, the bomb being set in a vacuum jar held in a $-15°$ brine bath, and the needle valve being left open. In these circumstances the evaporation of ammonia was so slow that no replenishment was needed. The swelling of spruce chips in liquid ammonia was investigated in the same way, each chip being carefully measured with dividers and identified with a metal tag. After immersion for 22 hr., the chips were removed and quickly measured, allowed to stand for another 22 hr. in the air, and measured again.

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A REDETERMINATION OF THE RELATIVE ENTHALPIES OF AQUEOUS PERCHLORIC ACID SOLUTIONS FROM 1 TO 24 MOLAL[1]

By D. R. Bidinosti[2] and W. J. Biermann

ABSTRACT

Previous tabulations of enthalpies of formation of perchloric acid solutions are not in agreement with the behavior expected for an acid as highly dissociated as perchloric acid. Measurements of the heats of neutralization of perchloric acid solutions with sodium hydroxide solutions were made and new values of the relative apparent partial molal enthalpies of perchloric acid solutions in the range 1 to 24 molal were computed from these. These new values agree with the anticipated behavior of perchloric acid.

Traditionally, any deviations of strong electrolyte solutions from ideal behavior are explained in terms of interionic attraction, dissociation of structures, and solvation of the ions produced in dissociation. Considering their effects on the heat of dilution, the first two will tend to make the process endothermic, while the third is an exothermic process. Lacking both theoretical and experimental information about the interionic attraction effects in concentrated electrolyte solutions, one can adopt as a working hypothesis the fact that, as a first approximation, for a given electrolyte type, heat of dilution contributions from these effects will be a function only of ionic strength but not of the specific nature of the electrolyte. Specific differences in heats of dilution of strong electrolyte solutions will then be explainable as differences in hydration and degree of dissociation. This view is confirmed by the similarity of the relative enthalpies of solutions of salts of the larger alkali metal ions with large anions (7), where we anticipate little hydration and complete dissociation.

Such a simplified picture is consistent with the tabulated values of the heats of formation of nitric acid solutions (5). Nitric acid is known to be incompletely dissociated even at relatively low concentration (8, 9), so that on dilution an appreciable number of protons are dissociated and upon hydration liberate sufficient energy that the over-all heat of dilution of nitric acid is exothermic at all concentrations appreciably removed from infinite dilution.

Perchloric acid is a much stronger acid than nitric acid. Undissociated perchloric acid can be detected at high concentrations, but below the vicinity of eight molal the concentration of undissociated molecules is too low to be detected (10). At very high concentrations it is to be expected that perchloric acid will resemble nitric acid in showing a substantially exothermic heat of dilution to infinite dilution, but in the vicinity of eight molal, as protons cease to be made available in quantity for the exothermic solvation process, there

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[2]*Holder of a National Research Council Bursary.*

should be a marked tendency for the process to become less exothermic. At lower concentrations it would appear necessary for the heat of dilution of perchloric acid to become markedly endothermic and, in fact, resemble such salts as sodium or potassium chloride, since, once dissociation is complete, thermal effects on dilution must be due almost entirely to interionic attraction.

The tabulated values of the heats of formation of perchloric acid solutions (2, 5) are quite different from this expectation, indicating the process to be exothermic down to about three molal and then to become endothermic by merely a few calories per mole. Because these older values could not be rationalized, they were suspect and a re-examination of the heat of dilution of perchloric acid solutions was indicated.

EXPERIMENTAL

The relative apparent partial molal enthalpies of perchloric acid solutions at various concentrations were determined indirectly by measuring the heat of neutralization of perchloric acid solutions by sodium hydroxide solutions of the same concentrations. The apparatus and technique have been described previously (1, 4).

A stock solution of carbonate free sodium hydroxide was prepared, diluted, and analyzed gravimetrically as in the earlier neutralization work. Reagent grade perchloric acid was used without further attempts at purification, and analyzed by weight titration against a gravimetrically standardized sodium hydroxide solution. Care was taken that the difference in concentration of a given acid–base set was as small as possible because of a lack of the data required to make exactly the small correction for concentration difference. Similarly, all neutralizations were started at a temperature within a few hundredths of a degree of 25.00° C., because there is insufficient heat capacity data to calculate the temperature coefficient of the reaction. In the concentration region studied, the difference in composition of the vapor phase before and after the reaction leads to heat effects of negligible magnitude. The experimental results of the heat of neutralization observations are recorded in Table I.

CALCULATION

The relative apparent partial molal enthalpy of the perchloric acid solution at the molality m, $\Phi_L(HClO_4, m)$, is then related to its heat of neutralization ΔH_N by sodium hydroxide of molality m by the relationship:

$$\Delta H_N = \Delta H_N^\circ + \Phi_L(NaClO_4, m') - \Phi_L(HClO_4, m) - \Phi_L(NaOH_4, m).$$

The molality of the reactants, m, is taken as the average of the closely adjusted acid and base concentrations, and m' is the concentration of the salt solution which results, related to m by

$$m' = 55.51\ m/(111.02 + m)\ .$$

The heat of neutralization at infinite dilution, ΔH_N°, was taken as $-13{,}321$ defined calories per mole (1). The values of the relative apparent partial molal

TABLE I

EXPERIMENTAL DATA FOR THE HEAT OF NEUTRALIZATION OF PERCHLORIC ACID AND SODIUM HYDROXIDE SOLUTIONS AT VARIOUS MOLALITIES

m ($HClO_4$)	m (NaOH)	ΔH_N, def. cal. 25.0°C.
24.299	24.291	24,086 24,089
20.081	20.099	21,822 21,851
16.083	16.090	19,474 19,476
13.411	13.410	17,824 17,834 17,837
11.233	11.221	16,626 16,627
9.193	9.195	15,633 15,628
7.860	7.856	14,980 14,982
6.080	6.103	14,317 14,301
5.008	5.018	14,032 14,034
4.020	4.014	13,673 13,684
2.524	2.538	13,478 13,485 13,470
1.012	1.011	13,381 13,383 13,401

enthalpies of sodium perchlorate solutions have been determined by Colomina and Nicolas (6). The relative apparent partial molal enthalpies of sodium hydroxide solutions are taken from Bertetti and McCabe (3), whose data were converted to defined calories per mole at 25° C. and corrected for an extrapolational error due to inclusion of Richards and Gucker's (11) low concentration data.

Table II presents smoothed values of the heat of neutralization of sodium hydroxide and perchloric acid solutions at integral concentrations, obtained by applying an approximately fitting analytic function and deviation curve to the original data. Included are the relative apparent partial molal enthalpies of the perchloric acid solutions and the partial molal enthalpy of perchloric acid at integral concentrations, together with the supplementary data used in their computation.

TABLE II

HEAT OF NEUTRALIZATION OF NaOH WITH $HClO_4$ AT INTEGRAL CONCENTRATIONS, AND ENTHALPIES OF PERCHLORIC ACID SOLUTIONS, AT 25°C. IN DEFINED CALORIES PER MOLE

m (reactant molality)	m product molality	$-\Delta H_N$	$\Phi(NaOH, m)$	$-\Phi(NaClO_4, m)$	$\Phi(HClO_4, m)$	$\Phi_2(HClO_4, m)$
1	0.4955	13,380	82	271	−295	−390
2	0.09823	13,440	8	481	−380	−540
3	1.460	13,510	−21	664	−455	−640
4	1.930	13,675	4	836	−500	−500
5	2.392	13,955	69	985	−420	150
6	2.846	14,280	167	1115	−325	420
7	3.293	14,665	303	1217	−180	765
8	3.731	15,090	474	1316	−25	1150
9	4.163	15,540	677	1412	125	1570
10	4.587	16,010	906	1491	295	2040
11	5.004	16,515	1162	1558	475	2565
12	5.415	17,040	1435	1617	670	3150
13	5.819	17,595	1729	1673	875	3790
14	6.217	18,180	2019	1725	1115	4520
15	6.608	18,785	2319	1774	1370	5325
16	6.993	19,415	2615	1820	1660	6215
17	7.372	20,015	2909	1862	1925	7010
18	7.745	20,605	3194	1902	2190	7085
19	8.113	21,200	3476	1936	2470	7560
20	8.475	21,785	3741	1967	2755	8035
21	8.831	22,290	2995	1995	2975	8435
22	9.182	22,805	4239	2020	3225	8855
23	9.528	23,345	4475	2044	3505	9305
24	9.868	23,920	4696	2062	3840	9795

DISCUSSION

The discrepancy between the Berthelot results and those of the present work is substantial, as shown in the selected values of Table III. We are inclined to

TABLE III

COMPARISON OF THIS WORK WITH THE EARLIER VALUES

Molality	Defined calories per mole	
	Berthelot	This work
2	−20	−380
3	−10	−455
4	5	−500
8	220	−25
9	305	125
15	880	1370

prefer the results of the present work because previous experience with the neutralization measurements, as well as an analysis of contributing errors, indicates that the maximum error in the heat of neutralization values is not apt to be greater than 20 calories per mole. The auxiliary data used in computing the relative apparent partial molal enthalpy of perchloric acid could not account for a significant portion of the discrepancies of Table III.

The results of this work agree satisfactorily with the anticipated behavior of perchloric acid on dilution, showing a rapid curtailment of the exothermic process in the region where dissociation is known to be effectively complete, and below this region resembling the "strong" salts much more closely than it resembles nitric or other weaker acids in its heat of dilution properties.

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THE REACTION OF TETRAMETHYLTHIURAMDISULPHIDE WITH ACETONE

I. REACTION PRODUCTS[1]

By J. R. Robinson,[2] David Craig,[3] and Ray B. Fowler[3]

ABSTRACT

Tetramethylthiuramdisulphide reacts with acetone to form various dithiocarbamate derivatives of acetone, dimethylamine, and carbon disulphide. The reaction has an induction period which is markedly influenced by various additives. The reaction products, their properties and synthesis, are described.

Tetramethylthiuramdisulphide, "TMTD" or "*bis*-(dimethylthiocarbamoyl)-disulphide", is well known as a vulcanization accelerator and as a potent fungicide. In handling hot acetone solutions of the material we have observed evidence of rapid decomposition; even at room temperature, discoloration occurs in a few hours. A survey of the literature indicates that other workers have noted this instability (4, 5, 7, 8) but no one appears to have reported on the composition of the reaction products. An investigation of the process was considered worth while as it might help to elucidate the chemical behavior of TMTD as an accelerator and a fungicide.

DISCUSSION

We have found that TMTD (I) reacts with refluxing acetone to form 1-(dimethylthiocarbamoylthio)-2-propanone (II), dimethylammonium dimethyldithiocarbamate (IV), dimethylamine, carbon disulphide, 1,3-*bis*-(dimethylthiocarbamoylthio)-2-dimethylamino-1-propene (V), and 1,3-*bis*-(dimethylthiocarbamoylthio)-2-propanone (VI). There was no evidence of a 1,1-isomer of VI, and we were unable to isolate the expected monosubstituted propene, VII. The enamine (V) readily hydrolyzes to the propanone derivative VI.

Several grades of acetone were tried including material purified through the bisulphite compound, "Spectro Grade", "Certified Reagent Grade", and commercial amine-free acetone (Carbide and Carbon Chemical Corporation, C.P. grade). The latter material was used for the experiments reported here, as all grades gave the same products. In paper II of this series (3) (Table I), the effect of water upon the reaction is shown to be relatively small, so no attempt was made to dry the acetone.

On the basis of earlier studies of the TMTD vulcanization of rubber (1, 2) we also expected to find sulphur, tetramethylthiurammonosulphide, dimethyl-

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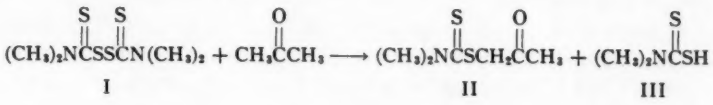
[2]*Science Service Laboratory, Canada Department of Agriculture, University Sub Post Office, London, Ontario.*
[3]*The B.F. Goodrich Research Center, Brecksville, Ohio.*

thiocarbamoyldimethylsulphenamide, and tetramethylthiourea; none of these materials was found, nor was acetonylacetone.

We were unable to form the disubstituted compound VI by treating the monosubstituted acetone (II) with excess TMTD in dry benzene; similarly, the reverse attempt to form II by refluxing VI with acetone failed. Attempts to synthesize the propene derivative (V) by treatment of VI with dimethylamine in the presence of dehydrating agents were unsuccessful.



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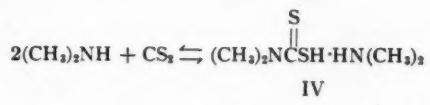

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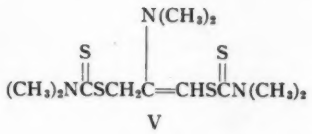

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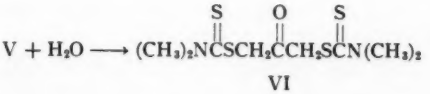

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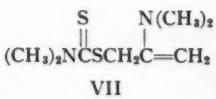

VII

The structures of the mono- and di-substituted acetones (II and VI) were confirmed by synthesis from the appropriate chloro- and bromo-acetones, using the method of Nachmias (6) who reported II but not VI.

The TMTD–acetone reaction exhibits an induction period the length of which can be completely controlled by the use of suitable additives. The most potent activator of the reaction is dimethylamine, or its salt, dimethylammonium dimethyldithiocarbamate (IV). Since most samples of TMTD contain varying amounts of IV as an impurity, different induction periods will be noted with different samples, as the influence of IV is proportional to its concentration. The addition of acetic anhydride, on the other hand, will inhibit the reaction indefinitely. A more detailed study of the influence of additives may be found in paper II of this series.[4]

[4]*See the next paper in this Journal.*

EXPERIMENTAL

1-(Dimethylthiocarbamoylthio)-2-propanone (II)

A mixture of 24.0 gm. (0.1 mole) of TMTD and 60 ml. of benzene was refluxed for 2.5 hr. during the addition of 6.4 gm. (0.11 mole) of acetone. Refluxing was continued for one hour. The mixture was cooled to 10° and filtered to give 6.6 gm. of dimethylammonium dimethyldithiocarbamate (IV) which melted at 131–135° with decomposition. The filtrate, containing CS_2, was distilled until nearly all the benzene was removed. The addition of ether caused the slow crystallization of Crop 1, 0.5 gm., m.p. 150–152°. The filtrate on evaporation gave 4.5 gm. of solid (Crop 2), which melted at 47–50° and at 58° after crystallization first from water and then from alcohol–water mixture. Anal. Calc. for $C_6H_{11}NOS_2$: C, 40.63; H, 6.26; N, 7.90; S, 36.18%. Found: C, 40.50; H, 6.26; N, 7.89; S, 36.24%.

The compound thus analyzes for 1-(dimethylthiocarbamoylthio)-2-propanone or "acetonyldimethyldithiocarbamate" (II), a compound reported by Nachmias (6) as the reaction product of sodium dimethyldithiocarbamate and monochloracetone. Using his method, we secured II in 90% yield, melting at 58° alone or mixed with the II from Crop 2 above. We have not observed the melting point of 73° reported by him. Dr. A. Quevauviller has forwarded to us a sample of the Nachmias compound. We found it to melt at 58° alone or mixed with our II. The material fails to give the iodoform test. It is soluble in hot water and most organic solvents.

1,3-bis-(Dimethylthiocarbamoylthio)-2-propanone (VI)

The filtrate from Crop 2 (above), on standing, deposited a further 0.6 gm. of crystals melting at 150–152° alone or mixed with Crop 1. Recrystallization from alcohol gave colorless needles, m.p. 158°. Anal. Calc. for $C_9H_{16}N_2OS_4$: C, 36.45; H, 5.43; N, 9.45; S, 43.25%. Found: C, 36.55; H, 5.42; N, 9.34; S, 43.19%.

This compound is quite soluble in benzene, slightly soluble in alcohol, and nearly insoluble in hexane, water, and ether. Samples prepared by the method of Nachmias (6) from 1,3-dihalo-2-propanones melted at 158° alone or mixed with VI from Crop 1 above.

Significantly higher yields of both II and VI were later obtained by eliminating the benzene and simply refluxing an acetone solution of TMTD. After an initial induction period, the same products were formed. The reaction was greatly accelerated (shown by earlier color development, amine and CS_2 formation) by the addition of a crystal of dimethylammonium dimethyldithiocarbamate. The acetone was then evaporated, the products extracted from the residue with appropriate solvents and recrystallized as described above.

1,3-bis-(Dimethylthiocarbamoylthio)-2-dimethylamino-1-propene (V)

In some experiments, difficulty was encountered in separating II from VI and resort was made to alcohol for crystallization. Needles mixed with well-defined granular crystals appeared. The granules (V) were separated (physic-

ally) from the needles (VI) and, after two recrystallizations from alcohol, they melted at 102–103°. Anal. Calc. for $C_{11}H_{21}N_3S_4$: C, 40.83; H, 6.55; N, 12.98%. Found: C, 40.68; H, 6.61; N, 12.55%.

Conversion of V to VI

Compound V, 0.0605 gm., 2 ml. of alcohol, and one drop of aqueous acetic acid were refluxed for two minutes and the solvent evaporated. Recrystallization of the residue gave 0.054 gm. (98%) of colorless needles, m.p. 156–158° alone or mixed with VI.

Acetone and VI

A solution of 262 mgm. (0.883 mmole) of VI in 20 ml. of acetone was refluxed for 24 hr. It was cooled and the acetone evaporated under a stream of nitrogen. The residue was recrystallized from ethanol resulting in a 95% recovery of VI, m.p. 156–157°.

A similar experiment in which 15.4 mgm. (0.092 mmole) of dimethylammonium dimethyldithiocarbamate was included produced the same result. Obviously VI is not readily converted to II in excess acetone.

Tetramethylthiuramdisulphide (TMTD) and II

A solution of 240 mgm. (1.0 mmole) of TMTD and 177.3 mgm. (1.0 mmole) of II in 15 ml. of dry benzene was refluxed for 20 hr. On evaporation of the solvent, II was first recovered from the residue by leaching with warm water, producing needles, m.p. 56–58°. The final residue was then recrystallized from ethanol and 220 mgm. (92%) of TMTD, m.p. 156–157° alone or mixed with an authentic sample, was recovered.

Another run which included 3.8 mgm. (0.02 mmole) of dimethylammonium dimethyldithiocarbamate gave similar results. In neither case was there any evidence of the production of compound VI from II.

Attempted Synthesis of V

Compound VI, 381 mgm. (1.28 mmole), was dissolved in 500 ml. of absolute ethanol and treated with a large excess (25 ml.) of anhydrous dimethylamine. Anhydrous $MgSO_4$, 15 gm., was added and the suspension was placed on the shaker for 30 hr. at room temperature. After it was allowed to stand an additional 1½ days, the drying agent was filtered off and the solvent and excess dimethylamine evaporated under dry nitrogen. The residue consisted of 360 mgm. of starting material, m.p. 156°. Refluxing with K_2CO_3 gave similar results.

Spectra

Absorption spectra of some of the products are given below.

The significant infrared absorption peaks[5] of chloroform solutions of II, IV,

[5] *The infrared data were obtained using a Perkin-Elmer No. 21 double beam recording spectrophotometer. The authors are indebted to Mr. R. W. White, Science Service Laboratory, for recording these data.*

and VI are as follows, where S, M, and W indicate a strong, medium, and weak absorption:

$$II = (CH_3)_2NC(=S)CH_2C(=O)CH_3$$

2920M, 1715S, 1495S, 1407W, 1380S, 1357S, 1277W, 1225*, 1150S, 1050W, 980S, 867W cm.$^{-1}$

$$IV = (CH_3)_2NC(=S)SH\cdot HN(CH_3)_2$$

2920S, 2670S, 2390M, 1485M, 1465S, 1410W, 1365S, 1245S, 1215*, 1120S, 1040W, 1025M, 967S, 890M, 660W cm.$^{-1}$

$$VI = (CH_3)_2NC(=S)CH_2C(=O)CH_2SC(=S)N(CH_3)_2$$

2920M, 1717M, 1495S, 1407W, 1380S, 1290W, 1225*, 1147S, 1040M, 982S, 895M cm.$^{-1}$

A value marked with an asterisk is approximate, the exact peak being partially obscured by one due to chloroform.

The peak at 1357 cm.$^{-1}$ is due to the $CH_3C(=O)$—group and its presence in II and absence in VI confirms the symmetrical structure of VI.

In the near infrared[6] region of the spectrum freshly prepared acetone solutions of I, II, IV, VI, dimethylamine, and sodium dimethyldithiocarbamate exhibit no absorption. After two weeks at room temperature absorption peaks occur at 2620–2680, 2195, 2060, 1925, 1775, 1725, and 1435 millimicrons in all of the solutions. A similar absorption spectrum is obtained from acetone which has been refluxed with barium hydroxide, a procedure known to favor the production of diacetone alcohol.

In the ultraviolet region,[6] freshly prepared ethanol solutions of II, IV, and VI exhibit strong absorption with maxima at the following wavelengths:

IV: 289 and 254 millimicrons, both of which disappear when the solutions are left overnight at room temperature.

II and VI: 276, 246, and 216 millimicrons. These solutions appear to be stable.

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[6]*Ultraviolet and near-infrared data were obtained using a Beckman DK-1 recording spectrophotometer.*

THE REACTION OF TETRAMETHYLTHIURAMDISULPHIDE WITH ACETONE

II. THE EFFECTS OF ADDITIVES[1]

By David Craig,[2] J. R. Robinson,[3] and Ray B. Fowler[2]

ABSTRACT

A discussion of the effects of additives upon the reaction of tetramethylthiuramdisulphide with acetone leads to the suggestion that the process is autocatalytic, that dimethylamine is the natural catalyst, and that the time required for its formation describes the induction period. The formation of the various products of the reaction is explained in terms of a free-radical mechanism.

The preceding paper (6) has cited the products which have been isolated from the reaction of tetramethylthiuramdisulphide (TMTD) with acetone. It was pointed out that the process exhibits an induction period, and it is the purpose of the present work to report on the effects of various additives upon this phenomenon and thence to draw certain conclusions regarding the probable course of the reaction.

Tetraethylthiuramdisulphide (Antabuse) is shown to be relatively stable towards acetone.

DISCUSSION

A. The Effects of Additives

All additives studied exerted their effect, if any, upon the rate of the reaction, the length of the induction period, and in one or two instances, the yields of the products. At no time did we observe a change in the chemical nature of the products. The reaction rates, product analyses, and a rough estimation of induction periods were studied using the macrotechniques described below. In order to extend the induction period and thus magnify its response to various additives, dilute solution studies were inaugurated and the reaction followed spectrophotometrically. The details of these are also to be found in the experimental part.

Among the additives which shorten the induction period are strongly basic primary and secondary amines and acetic acid. Relatively inactive or inert materials are weak nitrogen bases, water, sulphur, carbon disulphide, and tetramethylthiurammonosulphide. Inhibiting action was displayed by zinc oxide, acetic anhydride, and triethylamine. The latter seemed to shorten the induction period, but markedly slowed the reaction rate. Pyridine, a weak base, had little effect. Diphenylamine had no effect. Zinc oxide, in dilute solution, had no effect upon the induction period and yet this substance, which

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[2]*The B. F. Goodrich Research Center.*
[3]*Science Service Laboratory, Canada Department of Agriculture.*

may be regarded as an insoluble base, effectively prevented the reaction in concentrated solution (Table I, expt. 17). It may be presumed, therefore, that the distance to the basic surface of the zinc oxide is simply too great, in dilute solution, for effective neutralization of the catalyst.

TABLE I

INDUCTION AND REACTION PERIODS AND MOLES OF REACTION PRODUCTS FOR THE REACTION OF 1.5 MOLES OF ACETONE, 0.1 MOLE OF TMTD, AND VARIOUS ADDITIVES

Expt. No.	Additive	Moles	Induction period, min.	Reaction period, min.	Products					II
					CS_2	IV	II	VI	V	VI+V
1	None	—	50	50	0.045	0.038	0.054	0.012	—	4.5
2[a]	None	—	175	45	.047	.049	.061	.013	—	4.7
3	Me_2NH	0.022	0	20	.047	.037	.059	.009	0.009	3.3
4[a]	Me_2NH	.0055	0	40	.036	.057	.074[d]	.008	—	9.3
5[a]	Et_3N[b]	.044	80	240	.034	.024	.043[d]	.024	—	1.8
6	Et_3N[c]	.022	50	145	.040	.036	.047	.021	—	2.2
7	C_5H_5N	.10	50	50	.053	.043	.058	.013	—	4.5
8[a]	Et_3N, Me_2NH	.044 .011	12	30	.037	.052	.045	.020	—	2.3
9[a]	Et_3N, IV	.004 .011	28	110	.034	.052	.052	.016	.007	2.3
10[a]	HOAc	.0067	15	40	.055	.050	.085	.004	—	21.0
11	CS_2[g]	.0053	83	48	.058	.040	.066[d]	.016	—	4.1
12	Sulphur	.12 gm.	87	45	.060	.044	.047[d]	.017	—	2.8
13[a]	TMTM[f]	.011	115	45	.053	.041	.071	.015	—	4.7
14[a]	II	.10	50	30	.053	.039	.041	.010	.005	2.7
15[a]	H_2O	.056	140	60	.053	.037	.073[d]	.013	—	5.6
16[a]	Me_2NH_2Cl	.011	50	60	.050	—	—	—	—	—
17	ZnO[e]	.20	>180	No reaction occurred						
18	Nitrogen stream	—	—	No reaction occurred						

[a]*Freshly crystallized TMTD, m.p. 161–162°, was used in this run. Material, m.p. 159–161°, was used in other runs.* [b]*Et_3N distilled from P_2O_5 but nevertheless contained 0.7% Et_2NH.* [c]*Et_3N contained 2% Et_2NH.* [d]*HOAc was used during isolation to convert enamines to ketones.* [e]*0.02 mole of TMTD was used and was recovered unchanged.* [f]*Tetramethylthiurammonosulphide.* [g]*The quantity of CS_2 added was not sufficient to interfere with the measurement of the induction period.*

Acetic anhydride, in the presence or absence of acetic acid, was an effective inhibitor. In the former case, about one per cent of tetramethylthiurammonosulphide was formed, revealing, presumably, the tendency of TMTD to dissociate into more stable substances. This monosulphide, when refluxed with acetone alone, was very slowly converted to tetramethylthiourea and carbon disulphide. It had a rather small effect, possibly due to trace impurities, on the induction period of the TMTD–acetone reaction but no effect on the rate. However, sulphur, an expected product along with tetramethylthiurammonosulphide from the decomposition of TMTD, sometimes shortened the induction period, sometimes lengthened it, as in experiment 12; the rate was unaffected. Table V shows how the inhibitory effect of acetic anhydride may be offset by the addition of an equivalent amount of dimethylammonium dimethyldithiocarbamate (IV).

The use of reagents such as acetic anhydride and zinc oxide to bind liberated dimethylamine chemically is presumably no more effective than purely phys-

ical methods for removing this amine as fast as it is formed. Thus, there was little or no reaction in the concentrated solutions when acetone was allowed to escape slowly from the system, sweeping the amine out with it. An even more effective method was to pass a slow stream of nitrogen or air through the reflux above the system. This technique produced equally impressive results in the dilute solution studies (Table II).

TABLE II

EFFECT OF BASES ON THE INDUCTION PERIOD OF 12.5 MGM. (0.052 MM.) OF TMTD IN 20 ML. OF ACETONE

Base	(pK_H)[a]	mM. added	Induction period
Di-*n*-butylamine	(11.31)	0.01	240 min.
		0.06	60 "
		0.1	50 "
		0.2	30 "
Diethylamine	(10.98)	0.02	110 "
		0.04	50 "
		0.1	30 "
Dimethylamine	(10.71)	0.01	40 "
		0.02	25 "
		0.04	5–10 "
Dimethylammonium dimethyldithiocarbamate	(10.71)	0.004	50 "
		0.009	25 "
		0.02	5–10 "
Ammonia	(9.27)	0.06	90 "
		0.12	60 "
		0.36	25 "
		0.47	5–10 "
Pyridine	(5.26)	0.1	17 hr.
Triethylamine	(10.74)	0.006	15 "
		0.1	11.5 "
		0.2	8 "
Diphenylamine	(0.85)	0.1	20 "
Zinc oxide	— (Suspension)	0.001	20 "
Acetic acid	—	0.2	6 "
		0.4	6 "
		0.8	6 "
Reference solution	—	—	20 "
" " (under nitrogen stream)		—	>70 "

[a] pK_H *values: Hall, N. F. and Sprinkle, M. R. J. Am. Chem. Soc. 54: 3469. 1932.*

The dilute solution study also shows that dimethylammonium dimethyldithiocarbamate (IV) is a particularly effective activator of the reaction. It would appear that IV, at low concentration, is completely dissociated into dimethylamine and carbon disulphide, as in equation 4, p. 1606. It is equally evident that the effectiveness of the stronger nitrogen bases is proportional to their concentration.

The data of Table III indicate the effect of TMTD concentration on the length of the induction period in the absence of additives. A few data are

TABLE III

EFFECT OF CONCENTRATION OF TMTD ON THE INDUCTION PERIOD IN 20 ML. ACETONE IN THE ABSENCE OF CATALYST

TMTD added, mM.	Induction period, hr.
0.052	20
0.10	15
0.25	12.5
0.50	10
1.0	5
2.0	3

presented in Table IV which compare the relatively stable *bis*-(diethylthiocarbamoyl)-disulphide (Antabuse) with TMTD, in the presence and absence of IV, in refluxing acetone.

TABLE IV

EFFECT OF DIMETHYLAMMONIUM DIMETHYLDITHIOCARBAMATE (IV) ON THE INDUCTION PERIOD OF 0.052 MM. OF TMTD OR ANTABUSE IN 20 ML. OF ACETONE

Weight of IV, mM.	Induction period	
	TMTD, min.	Antabuse, hr.
0	1200	150
0.004	50	25
0.01	25	20
0.02	5	3

TABLE V

EFFECT OF THE CONCENTRATION OF ACETIC ANHYDRIDE ON THE INDUCTION PERIOD OF 0.052 MM. OF TMTD IN 20 ML. OF ACETONE IN THE PRESENCE OR ABSENCE OF IV

Weight of Ac_2O added, mM.	Weight of IV added, mM.	Induction period, hr.
0	0	20
0.1	0	>150
0.01	0.01	1/3
0.03	0.01	>150

B. The Reaction Mechanism

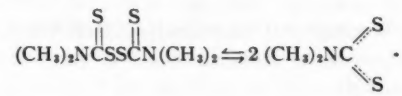
von Braun has reported on the decomposition of TMTD (1) and it appears that any compound RH, where H is sufficiently labile, may be expected to react as shown in equation 1, p. 1606. This may be the initiating step in the TMTD–acetone reaction (equations 2 and 3). We have observed that the rate of this reaction is relatively slow when the TMTD is highly purified, although

it varies with TMTD concentration (Table III). That dimethylamine is an effective promoter of the reaction is quite evident (Tables I, II, IV, V). Thus, in the absence of added amine, the reaction may be described as autocatalytic, and the induction period may be defined as the time required for the formation of the amine from TMTD. This conclusion is further supported by the observation that continuous removal of the amine, by chemical or physical means, results in an almost indefinite extension of the induction period (Tables I, II).

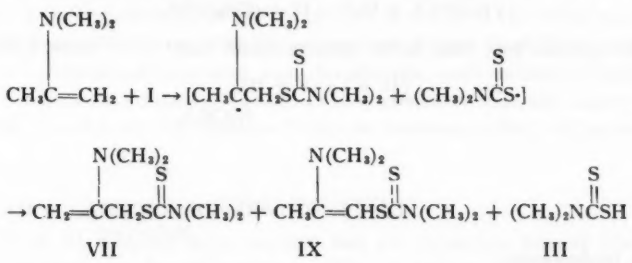
In order to explain the catalytic effect of dimethylamine, the presence of 1,3-*bis*-(dimethylthiocarbamoylthio)-2-dimethylamino-2-propene (V), as well as the absence of 1,1-*bis*-(dimethylthiocarbamoylthio)-2-propanone in the reaction residues, we are suggesting the course of reactions outlined by equations 5 to 9. The equilibrium described by equation 5 must be shifted far to the left, as earlier studies have shown (5) that, as a rule, aliphatic secondary amines and ketones do not readily form enamines in isolable amounts, even in the presence of dehydrating agents. Similarly, we were unable to prepare enamine V by treating the disubstituted acetone VI with dimethylamine.

If equation 5 is true, other amines with properties similar to those of dimethylamine (base strength, molecular size and shape, ability to form enamines, etc.) should also act as catalysts, and this is indeed the case (Table II). Within the strong-base group, there appears to be no correlation between pK_H values and observed effects. The pK_H values quoted, however, may have little significance for an acetone medium.

Equation 6 demonstrates the reaction of enamine VIII with further TMTD to form enamine VII,[4] thus regenerating dimethylamine through the unstable acid (III). Since TMTD is most likely to react as a resonance hybrid radical (4) it is convenient to assume a free-radical rather than an ionic mechanism:



The center of reactivity on the enamine VIII is likely to be similar to that of the corresponding enol (3) and the reaction with TMTD will be:[5]



VII IX III

[4] *The numbers assigned to the products are retained from Part I, and are not related to the sequence of the mechanism equations.*

[5] *The equations are not balanced; they are intended only to indicate the various radical species which may be present.*

1. $(CH_3)_2NC(=S)SSC(=S)N(CH_3)_2 + RH \rightarrow R{-}SC(=S)N(CH_3)_2 + (CH_3)_2NC(=S)SH$ (I; III)

2. $I + CH_3C(=O)CH_3 \rightarrow (CH_3)_2NC(=S)SCH_2C(=O)CH_3 + III$ (II)

3. $III \rightarrow (CH_3)_2NH + CS_2$

4. $2(CH_3)_2NH + CS_2 \leftrightarrows (CH_3)_2NC(=S)SH.HN(CH_3)_2$ (IV)

5. $(CH_3)_2NH + CH_3C(=O)CH_3 \leftrightarrows CH_3C(N(CH_3)_2)=CH_2 + H_2O$ (VIII)

6. $VIII + I \rightarrow (CH_3)_2NC(=S)SCH_2C(N(CH_3)_2)=CH_2 + III$ (VII)

7. $VII + I \rightarrow (CH_3)_2NC(=S)SCH_2C(N(CH_3)_2)(=S)CH=SCN(CH_3)_2 + III$ (V)

8. $VII + H_2O \rightarrow (CH_3)_2NC(=S)SCH_2C(=O)CH_3 + (CH_3)_2NH$ (II)

9. $V + H_2O \rightarrow (CH_3)_2NC(=S)SCH_2C(=O)CH_2SC(=S)N(CH_3)_2 + (CH_3)_2NH$ (VI)

10. $5\,I + 4CH_3C(=O)CH_3 \rightarrow 3\,II + 2\,IV + VI + 3CS_2 + (CH_3)_2NH$

Both VII and IX can react with water to give identical products:

$$VII\ \textit{OR}\ IX + H_2O \rightarrow II + (CH_3)_2NH.$$

It would appear, too, that both isomers could react with more TMTD:

$$VII + I \rightarrow V + III$$

$$IX + I \rightarrow CH_2{=}C(N(CH_3)_2){-}CH(SC(=S)N(CH_3)_2)_2 + III \quad (X)$$

and, on hydrolysis:

$$V + H_2O \rightarrow VI + (CH_3)_2NH$$

$$X + H_2O \rightarrow CH_3C(=O)CH(SC(=S)N(CH_3)_2)_2 + (CH_3)_2NH. \quad (XI)$$

However, since neither the unsymmetrical isomer XI nor any of its precursors was found in the residues, probably only VII reacts with TMTD. Presumably IX is completely removed by water or by rearrangement to VII.

Although neither of the enamines VII and VIII was isolated, their existence is postulated on the demonstrated presence of the higher molecular-weight (and apparently more stable) analogue (V). Also, it is only by assuming their formation that we can explain the facts reported in Part I, namely, that no 1,1-isomer of VI is found, that the monosubstituted acetone II is not an intermediate in the formation of the disubstituted VI, and that VI cannot be converted to II but is readily formed by the hydrolysis of V, as in equation 9. Furthermore, residues from which II and VI had been completely removed by crystallization were induced to produce much more of these materials by mild hydrolysis with dilute acetic acid. This clearly demonstrates the presence of both the intermediates V and VII.

As shown by equations 7, 8, and 9, products VI and II compete for the available enamine VII. Hence the ratio of these materials actually produced will vary largely with external influences, and the system is thus too complex to allow the writing of a simple stoichiometric equation. If we could assume complete conversion of IX to VII, an equal proportionation of VII, no loss of gaseous components, and equal rates for reactions 6 and 7, then the over-all process might be described by equation 10.

The action of triethylamine (Table I) lends further support to this mechanism. This base, somewhat like zinc oxide but less effective, stabilizes dimethylamine as the dithiocarbamate ion (2) and so lowers the reaction rate. It also depressed the production of II in favor of V+VI. By slowing down the over-all rate, the tertiary amine apparently allows reaction 7 to catch up with reaction 6, an effect which is markedly opposite to that of acetic acid. The shortening of the induction period by the tertiary amine is clearly a result of its contamination by a small amount of secondary amine; it cannot act catalytically because of its inability to form an enamine.

The catalyst effects of acetic acid are complex. In concentrated TMTD solutions it was a potent activator, but in dilute solution the effect was weak and independent of the acid concentration. Two opposing effects may be operative: (*a*) the suppression of the ionization of the acid III, thus leaving III available for dissociation into dimethylamine and carbon disulphide and (*b*) the formation of dimethylammonium ion. As dimethylammonium chloride was relatively inactive as a catalyst (Table I) it is assumed that the cation of this salt is inactive, and hence (*a*) appears to be the dominant effect in concentrated solution.

EXPERIMENTAL

The reaction of TMTD with acetone has an induction period which, for refluxing mixtures, can be estimated quickly by noting the time required to form carbon disulphide. Also, for mixtures in which the amount of TMTD exceeds its solubility (which is 0.028 mole of TMTD per 1.5 moles of refluxing acetone), the additional time required to effect complete solution gives an

indication of the reaction rate. This is true, for example, of a mixture containing a ratio of 0.1 mole of TMTD to 1.5 moles of acetone, and Table I shows the effect of additives on the induction period, reaction time, and product composition resulting from such a mixture. If the operations were carried out in this way with a 100 ml. flask fitted with a stirrer and a vacuum jacketed ¼ in. × 24 in. nichrome wire coil column, it was possible to measure the time elapsing prior to CS_2 evolution. The column was fitted with a total reflux-variable take-off head. The low boiling point (38°) of the acetone–CS_2 azeotrope containing 67% CS_2 makes this method sensitive for detecting the formation of CS_2 in the refluxing mixture, i.e. the *end* of the induction period. The *reaction period* was considered to be the elapsed time between the appearance of CS_2 in the distillate and disappearance of solid TMTD in the refluxing mixture.

The residues from experiments such as these were first distilled to recover the excess acetone and CS_2; the latter was estimated by mixing the distillate with two volumes of water and weighing the lower layer. The distilland was then cooled to cause part of salt IV to crystallize. The liquor from this was then evaporated to dryness in a nitrogen stream and the residue crystallized from ether. The first fraction consisted of a mixture of IV and VI, subsequently separated by extraction with ether at room temperature. Compounds II and VI sometimes seem to crystallize with unexpected slowness apparently as a result of the existence in the reaction mixtures of the easily hydrolyzable enamines V and VII. Thus the sulphur runs (e.g., expt. 12, Table I) gave oily reaction mixtures from which II and VI were removed in the usual way. Much larger amounts of these compounds crystallized after the addition of 5 ml. of acetic acid to the alcoholic solution of the filtrates. VI forms a eutectic with about 98% of II, which melts at 56°.

Experiment 18 was repeated in two different ways. In one, acetone was allowed to evaporate through the reflux condenser so that 10 gm. was lost during eight hours. The reflux temperature, 55.0°, showed that no CS_2 was being formed. In a second, a stream of nitrogen was admitted to the reflux stream above the fractionating column at a rate just fast enough to evaporate 15 gm. of acetone to a dry-ice trap during 4.5 hr. Dimethylamine but no CS_2 was detected in the condensate. In this experiment an additional 10 gm. of acetone had been added to the charge. Again the reflux temperature remained at 55.0°. The reaction mixture was worked up to give a 96% recovery of TMTD.

Solubility of TMTD

The solubility of TMTD, m.p. 161–162°, in refluxing acetone was determined as follows. Six grams of TMTD was placed in a two-necked, 100 ml. flask which contained a glass-covered stirrer magnet. The flask was fitted with a small reflux condenser and with a small stoppered overflow for decanting liquid. A 21.8 gm. portion of acetone was added and the mixture refluxed 10 min. with stirring and the supernatant, which was clear, decanted to a tared crystallizing dish and quickly evaporated to dryness on a hot plate, under a nitrogen stream. The procedure was repeated with two additional 21.8 gm.

portions and one 10.9 gm. portion of acetone. The extrahend remaining in the 100 ml. flask was quickly evaporated at reduced pressure to dryness between extractions. The weights and melting points of the extracts were respectively: 1.61 gm. (158–159°), 1.66 gm. (159–160°), 1.68 gm. (159–160°), and 0.85 gm. (158–159°). The final extrahend weighed 0.12 gm. and melted at 160–161°. Thus, 1.68 gm. of TMTD dissolves in 21.8 gm. of refluxing acetone. This corresponds to 6.70 gm. (0.028 mole) in 87.0 gm. (1.5 moles) of acetone, or approximately 61 gm. per liter of refluxing acetone.

Acetone and Tetramethylthiurammonosulphide

A solution of 6.4 gm. acetone (0.11 mole) and 20.8 gm. of the monosulphide in 60 ml. of benzene was refluxed for 40 hr. The mixture was then fractionated through a 0.25 in. × 16 in. coil column. The first fraction (4.36 gm.), b.p. 40–48°, based on its density, contained 3.5 gm. CS_2 and 0.86 gm. of acetone. The presence of carbon disulphide was confirmed by preparation of the piperidine derivative, m.p. in a sealed tube 170–172° alone or mixed with an authentic specimen. The next fractions were mainly benzene. The residue was crystallized from methanol to give 5.6 gm. of monosulphide, m.p. 107–109°. The filtrates were then evaporated in nitrogen and the residue extracted with water to give several fractions totalling 7.0 gm. and melting at 77–78°, alone or mixed with an authentic specimen of tetramethylthiourea.

Dilute Solution Studies

One batch of highly purified TMTD was used as a source for all the dilute solution studies and the experimental conditions were rigidly standardized so that the only variable in each run was the added catalyst. The reference solution consisted of 12.5 mgm. of TMTD (0.052 mM.) dissolved in 20 ml. of acetone, corresponding to about 2.9×10^{-4} mole of TMTD per 1.5 moles of acetone. A spectrum of the starting material (TMTD) was obtained at the beginning of each run and, as the solution was refluxed, samples were withdrawn at appropriate intervals and their spectra examined. It was found that the shape of the curve (optical density vs. wave length, see Fig. 1) would remain constant for a time and then, quite suddenly, would begin to change. The measured interval during which the spectrum remained constant was reproducible for a given mixture and was taken as the induction period. The data given in Tables II–V were obtained in this way. To ensure that the reaction had followed the expected course, each run was continued until the spectrum was formed and remained constant. The spectrum of each sample was recorded directly upon those preceding it; thus the earliest change in the shape of the curve was detected, and this was facilitated by scanning downward in wave length. Although not absolute values, the measured induction periods are comparable and they should reflect the relative effectiveness of the various additives as activators of the reaction.

In sampling, the reaction mixture was cooled and 50 lambdas (0.05 ml.) of solution was removed by micropipette. The acetone was completely removed from the sample at room temperature, *in vacuo*, and the residue was taken up in 3.5 ml. of absolute ethanol. With absolute ethanol in the reference cell, a

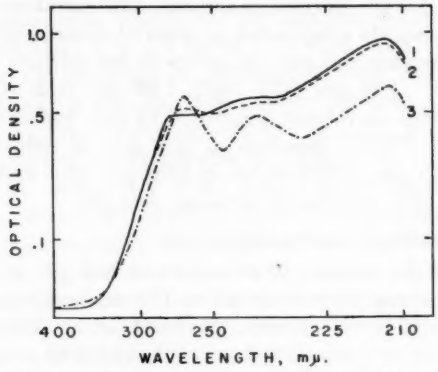


FIG. 1. The ultraviolet absorption spectra of: 1, TMTD at the beginning of the experiment; 2, the reaction products beginning to form at the end of the induction period; 3, the final products mixture.

Beckman recording spectrophotometer (Model DK-1) was used to obtain the spectrum in the ultraviolet region, 400–210 mμ. From the results shown in Table II it is seen that the reference solution has an induction period of 20 hr.

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INFRARED STUDIES OF SULPHUR-CONTAINING ORGANIC DERIVATIVES OF PHOSPHORUS PYROACIDS[1]

By R. A. McIvor, G. A. Grant, and C. E. Hubley

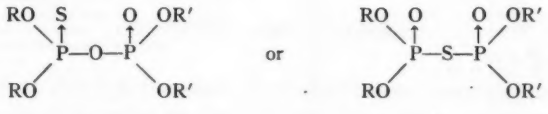
ABSTRACT

The assignments of several infrared bands of aliphatic phosphorus compounds have been reviewed and extended on the basis of new or improved data. These bands include POP, P → S, PSH, PSR, PH, and PCl. Several new assignments are proposed, mainly in the 12–24 μ region. Two examples are given of the application of these assignments to the determination of the structure of the thiopyrophosphates. It is shown that all procedures used for preparing monothiopyrophosphates yield exclusively the thiono isomer.

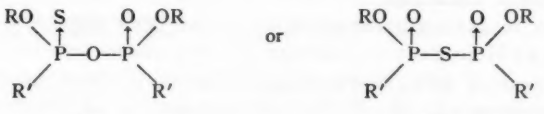
INTRODUCTION

In the course of studies on the chemistry of phosphorus pyroacids (6) extensive use was made of infrared spectra, both for determining the structure of the products and for assessing the purity of the intermediates. As the majority of the compounds were liquids, most of the spectra were determined as contact films. Although this method avoids solvent interference, no quantitative data on band intensities can be obtained directly.

The end products were I and II.



Ia *Ib*



IIa *IIb*

R′ and R = alkyl groups.

To determine which isomer was present, it was necessary to examine the spectra for the bands due to P → S, P—O—(P), P—S—(P), and RS, and to investigate the effects of environment on CH, P—O—(C), and C—O—(P) bands. From these studies it has been possible to make new assignments, some of which are well supported while others must be regarded as tentative.

EXPERIMENTAL

Preparation of most of the compounds examined is described elsewhere (6).

Unfortunately, it has not yet been possible to obtain all monothionopyrophosphates in a pure state. Chromatography has shown that the compounds

[1]*Manuscript received July 23, 1956.*
Contribution from the Defence Research Chemical Laboratories, Ottawa, Canada. Issued as D.R.C.L. Report No. 203A.

corresponding to spectra Nos. 1, 7, and 8 are probably at least 90% one substance, and because of their interest, the spectra have been included. Bands due to known impurities have been marked.

A Baird double-beam recording spectrophotometer was used for all spectra. Band positions are cited to the nearest 0.01 μ for sharp bands and to the nearest 0.1 μ for broad bands when possible.

Toxic compounds were sandwiched between small windows (approximately 25×10×2 mm.) and held in the microsample beam by a suitable holder. For decontamination the windows were dropped into alcoholic KOH. A macrocell was used for less toxic materials and decontamination was effected by washing the cell with a suitable solvent.

The two solid samples (spectra Nos. 25 and 36) were run as KBr pellets using a Hilger and Watts evacuable die. About 400 mgm. of KBr (ground to pass 200 mesh and dried in a vacuum oven at 50° C.) was mixed with 4 mgm. of sample in a hand mortar. The powder was then screened and pressed at 50° C. according to the die manufacturer's instructions.

Most spectra show overcompensation of atmospheric CO_2 absorption at 15 μ, an instrumental effect which always gives an inverted band and often distorts real bands in this region into false doublets.

RESULTS AND DISCUSSION

(*a*) P—O—P

Bergmann, Littauer, and Pinchas (2) assigned a band at 10.3–10.6 μ to P—O—P stretching, and report that it is not so apparent in the *n*-propyl and isopropyl esters. Corbridge and Lowe (3) note that this band shifts to longer wavelengths in polypyro compounds. It has been suggested in the above papers, and by Holmstedt and Larsson (5), that a band near 14.1 μ is associated with the P—O—P link. Mayhood and Harvey (7) have examined 14 compounds containing a P—O—P link and conclude that all absorb strongly in the 10.5–11.0 μ region, with the exception of tetramethyl pyrophosphate, which has a band at 10.3 μ (2) probably associated with the P—O—P link. They have also postulated* that when the P → O bond is replaced by P → S, the P—O—P band shifts to longer wavelengths and intensifies. They have been unable to assign any bands in the 14–15 μ region to the P—O—P linkage. Assignments are listed in Table I.

These data indicate that the 10.5–11.0 μ range suggested by Mayhood and Harvey should be extended downwards to 10.3 μ. This extension of the range discloses the possibility of confusing P—O—P compounds with those containing P—H and certain P—O—C groups (see below), so bands below 10.5 μ should be interpreted with caution. All the thiono compounds studied absorb at longer wavelengths than the corresponding oxygen compounds, and the P—O—P band is relatively more intense. In both the pyro and monothionopyro series the band shifts to longer wavelengths, as the alkyl group becomes larger, except in the ethyl compounds, which absorb at abnormally long wave-

**Unpublished data.*

TABLE I

ASSIGNMENTS FOR P—O—P, P → S, AND —P(→S)—X

Compounds	Ref.	Spectrum No.	Assignment in μ: P—O—P	P → S	S ↑ —P—X
Tetramethyl pyrophosphate	2		10.31		
Tetramethyl monothionopyrophosphate		1	10.38	12.02	
Tetraethyl pyrophosphate	7	2	10.62		
Tetraethyl monothionopyrophosphate		3	10.64	12.02	
Tetraethyl dithionopyrophosphate		4	10.72	11.99	
Tetra-*n*-propyl pyrophosphate		5	10.42		
Tetra-*n*-propyl monothionopyrophosphate		6	10.5	11.6(m) (?) 12.9(?) (wk)†	
Tetraisopropyl monothionopyrophosphate		7	10.53		
Tetra-*n*-butyl pyrophosphate	4		10.50		
Tetra-*n*-butyl monothionopyrophosphate		8	10.58	12.25	
Di-isopropyl dimethylpyrophosphonate	7		10.58		
Di-isopropyl dimethylmonothionopyrophosphonate		9	10.68	12.50	
Di(isopropyl methylphosphonothionyl) methylphosphonothioate		10	10.83	12.46	
Phosphorothionic trichloride	4			13.35*	13.35*
Methylphosphonothionyl dichloride		11		12.69	14.95
Dimethyl hydrogen phosphonothioate		12		12.6	15.25, 15.7
Dimethyl phosphorodithioic acid		13		12.82(?)	15.2
Methyl phosphorodichloridothionate		14		12.06	13.8, 14.2
Dimethyl phosphorochloridothionate		15		11.98	15.05
Trimethyl phosphorothionate	4			12.1	
OOS-Trimethyl phosphorodithioate		16		12.22(?)	15.2
Diethyl hydrogen phosphonothioate		17		12.98(?)	15.2, 15.7
Diethyl phosphorodithioic acid		18		13.03(?)	15.25
Diethyl phosphorothioic acid		19		12.65	
Ethyl phosphorodichloridothionate		20		12.52	13.75, 14.3
Diethyl phosphorochloridothionate		21		12.25	15.2
Triethyl phosphorothionate		22		12.12	
OOS-Triethyl phosphorodithioate		23		12.08	15.2
Triethyl phosphorotetrathioate		24		14.55*	14.55*
SS-Di-(diethyl phosphorothionyl)-*O*-ethyl phosphorotrithioate		25		12.05	15.5
Di-*n*-propyl phosphorochloridothionate		26		11.63(?) 13.07(?)	15.05
Isopropyl methylphosphonochloridothionate		27		12.58	15.9
Di-isopropyl methylphosphonothionate		28		12.60	15.3
Di-isopropyl phosphorochloridothionate		29		12.67	
Di-*n*-butyl phosphorochloridothionate		30		12.35	15.05

**These compounds have only one band in this region.*
†In this table and subsequently; s, strong; m, medium; wk, weak; sh, shoulder; br, broad.

lengths. This abnormality, which is more marked in the pyro series than the monothionopyro series, is probably due to perturbation by the intense band near 10.3 μ found in all ethyl esters of phosphorus acids, but not in esters containing other alkyl groups. Although most of the compounds exhibited bands in the 13–15 μ region, we were unable to establish any useful correlations in this region with the P—O—P linkage.

(*b*) P → S

According to Bellamy (1), all previous results confirm the view that the P → S absorption occurs in the 13–17 μ region, with considerable variation in intensity, sometimes being completely undetectable. However, almost all of the compounds prepared here are observed to have P → S bands in the 12–13 μ region. Assignments are listed in Table I. With few exceptions, these compounds show a strong band in the 11.9–12.7 μ region, although where several ester groups are present the P → S band may possibly be weak but superimposed on strong ester bands. Even then, however, there is usually little difficulty in selecting the appropriate band.

When halogen, mercapto, or alkylthio groups are attached to P the P → S

band shifts to slightly longer wavelengths, and a new, equally or more intense band appears in the 15 μ region (see below). The *n*-propyl esters examined showed no bands in this region, but two bands of medium or weak intensity near 11.6 μ and 13.0 μ. It is not definite which, if either, of these bands is associated with the P → S vibration, but the 13.0 μ band seems the more likely candidate (compare, for example, spectra 5 and 6). Two other exceptions to be noted are $PSCl_3$ and $PS(SEt)_3$, both of which exhibit only one band, at a position intermediate between the two bands normally expected in compounds of this type.

(*c*) —O—P—Cl, —O—P—S—, and R—P—Cl
(S) (S) (S)

Monochloro and monothiolo phosphorothionates exhibit a strong band near 15 μ. This band is shifted towards 14 μ, frequently with doublet formation in dichloro compounds. The corresponding phosphonochloridates and dichloridates absorb near 16 μ and 13 μ, respectively. In addition P(S)H compounds contain a weak doublet in this region which may arise, however, from the P—S—(H) stretching in the trivalent tautomer. $PSCl_3$ and $PS(SEt)_3$ are somewhat anomalous (see above). The wavelengths of maximum absorption for this band are given in Table I.

That this band should be due to P → S vibration seems improbable in view of the fact that in other than chloro compounds, the P → S seems to be nearer 12 μ, and in series of the type $ROPSCl_2$, $(RO)_2PSCl$, $(RO)_3PS$, a band is observed in the 12–12.6 μ region, which shifts gradually to shorter wavelengths. In compounds of the type —O—P—S—C the band might be attributed to the
(S)

C—S—(P) bond. This assignment also seems unlikely since compounds of the type —P—SH and —P—S—P—, which contain no C—S bonds, have a
(S) (S) (S)

similar band. We are unable to attribute this band to any particular vibration, but because of its intensity and location, it has proved exceedingly useful for identifying compounds or for assessing their purity.

(*d*) C—H *Deformation*

It was noted in this work that the shape of the CH deformation bands depends both on the nature of the alkyl group and the nature of the substitution, which observation can be very useful in determining the structure of a compound. It is well established (1) that CH_2 gives a band near 6.85 μ while CH_3 has an asymmetrical deformation at 6.9 and a symmetrical one at 7.27 and CH gives a weak band near 7.46 μ. Our assignments are as follows:

(1) MeO *bands.*—In phosphorus esters containing a methoxyl group, a single band appears at about 6.85 μ, which varies only slightly between MeO—P(O) and MeO—P(S). Small differences in shoulders of this band are noticed from compound to compound. P—Me groups do not have this band

but give rise to another band near 7.15 μ in both MeP(O) and MeP(S) compounds. Dimethyl methylphosphonate has both bands. In addition there is the well-known P(O)—Me absorption near 7.6 μ, which is shifted to 7.7 μ in P(S)—Me compounds.

(2) EtO *bands.*—Compounds containing an Et—O—P(O) link exhibit four characteristic bands, near 6.75, 6.92, 7.17, and 7.3 μ, usually increasing in intensity in that order. In compounds of trivalent phosphorus as well as in EtO—P(S) and EtO—P(O)—SR compounds, the 7.3 μ band disappears. EtS—P bands and Et—P bands are superimposed on these bands when present. EtS—P compounds containing no EtO absorb at 6.9, 7.05 (sh), 7.28, and 7.9 while Et—P compounds absorb at 6.85 and 7.15 μ.

(3) *n*-PrO *bands.*—On the basis of a few examples, the following tentative assignments have been made:
PrO—P(O): 6.77(sh), 6.82(s), 6.93(sh or wk), 7.18(m), 7.24(wk or sh), 7.4(v.wk). PrO—P(S): 6.82(s), 6.93(sh or wk), 7.18(m), 7.24(small sh). It is thus seen that the 6.77 shoulder and 7.4(v.wk) bands have disappeared in the P(S) compounds, and the 7.24 shoulder has diminished in intensity. No compounds containing P—Pr or P—S—Pr bands have been investigated.

(4) *i*-PrO *bands.*—Compounds containing *i*-PrO—P(O) bonds have bands at 6.78(sh), 6.81(m), 6.88(sh), 7.2 and 7.26 (strong doublet with 7.2 band slightly more intense), 7.39 μ (v.wk). In *i*-PrO—P(S) compounds the 6.78 shoulder disappears, the 6.88 shoulder becomes a band, the 7.26 μ band becomes considerably more intense than the 7.2 μ, and the 7.39 μ band is absent. The positions are almost identical for *n*-PrO and *i*-PrO bands, but the relative intensities differ. In *n*-PrO compounds the 6.8 μ band is about double the intensity of the 7.2 μ band whereas in *i*-PrO compounds the reverse is true.

(5) *n*-Bu *bands.*—The CH deformation bands for BuO—P(O) and BuO—P(S) compounds differ little, and are qualitatively the same as for PrO groups. BuO—P compounds give rise to bands at 6.77(sh), 6.82(s), 6.98(wk or sh), 7.2(wk.sh), 7.24(m). Substitution of P(S) for P(O) weakens the 6.77 μ shoulder, strengthens the 6.98 μ band, and weakens the 7.2 μ shoulder. BuO compounds differ from *n*-PrO compounds in a reversal of intensity of the 7.2 μ and 7.24 μ bands.

(6) *Cyclohexyloxy bands.*—$C_6H_{11}OP(O)$ compounds exhibit two very sharp bands at 6.88 μ and 7.28 μ with a small shoulder at 6.82 μ. No compounds containing $C_6H_{11}OP(S)$ have yet been investigated.

(*e*) *The* C—O—(P) *and* P—O—(C) *Vibrations*

As these bands are usually very intense they have been fairly extensively investigated (1, 4, 7). The usual assignments for C—O—(P) are in the 8.4–9.0 μ region and for P—O—(C) from 9.5 to 10.5 μ. The former are sharp and of medium intensity, while the latter usually give rise to a broad, very strong, complex absorption between 9.5 and 10.5 μ. Other bands, due to P—H, P—OH, P—SH, C—C, C—C—O, and C—N, may also fall in this region, increasing the complexity of the band. It is worth while, however, to discuss these bands

individually, emphasizing the effects of various alkyl groups and environment of the phosphorus atom.

(1) MeO *compounds*.—Compounds containing a MeOP linkage show a sharp band of medium intensity near 8.4 μ and a very strong broad band between 9.5 and 9.85 μ. In MeOP(O) compounds, the lower band is found between 8.4 and 8.43 μ, and the longer wavelength band near 9.5 μ. In MeOP(S) compounds, the corresponding bands are near 8.45 μ and 9.7 μ, while in trivalent MeOP compounds the latter band is near 9.85 μ.

(2) EtO *compounds*.—Compounds with ethoxy groups attached to phosphorus exhibit a sharp band of medium intensity from 8.56 to 8.60 μ, in EtOP(O) compounds, and from 8.58 to 8.62 μ in EtOP(S) and trivalent compounds. As the number of ethoxyl groups increases from one to three this band shifts slightly to shorter wavelengths. A weak band occurs between 9.03 and 9.1 μ, usually at 9.05 μ, in all types of EtO—P compounds. The next band at longer wavelengths in all EtO—P compounds is between 9.65 and 9.72 μ for EtO—P(O) and trivalent compounds, and between 9.7 and 9.9 μ for EtO—P(S) compounds. This band also shows a slight shift to shorter wavelengths as the number of ethoxy groups increases. Another band appears between 10.1 and 10.6 μ whose intensity varies markedly with the number of ethoxy groups, and which shifts toward longer wavelengths as the number of ethoxy groups increases, or when P—R or P—S—R groups are present. EtO—P(O) compounds absorb in the 10.1–10.3 μ region, EtO—P(S) compounds from 10.2 to 10.6 μ, and trivalent EtO—P compounds near 10.9 μ.

(3) *n*-PrO *compounds*.—A weak band is found in these compounds near 8.65 μ, as well as shoulders near 9.1 μ and from 9.4–9.5 μ regardless of the environment of the phosphorus atom. The P—O—(C) absorption is between 9.80 and 9.85 μ in PrO—P(O) compounds and at 9.98 μ in the one PrO—P(S) compound examined.

(4) *i*-PrO *compounds*.—Isopropoxy compounds have three very characteristic sharp bands of medium intensity at 8.45 μ, 8.7 to 8.72 μ, and 8.98 to 9.02 μ. The P—O—(C) band occurs between 9.88 and 10.1 μ in all cases. In addition, most compounds containing a P—C link have an additional band in the 10.15–10.25 μ region.

(5) *n*-BuO *compounds*.—These compounds have two very weak bands at 8.68 and 8.9 μ, a shoulder or band between 9.3 and 9.4 μ, and a very strong, broad band between 9.65 and 9.8 μ (usually about 9.7 μ). P—C compounds have an additional band at 10.2 μ and tributyl phosphite one at 10.4 μ.

(6) *Cyclohexyloxy compounds*.—The few compounds examined have weak bands at 8.62 and 8.85 μ, a band or shoulder at 9.6 μ, a strong band at 9.8 μ, and tricyclohexylphosphite has an additional strong band at 10.25 μ.

In summary, the C—O—(P) band is most characteristic of the alkyl group, although the P—O—(C) does show environmental changes for the lower molecular weight groups. Trivalent compounds either show a bathochromic shift of the P—O—(C) band or have a new band at longer wavelengths.

(*f*) *The* P—H *Vibration*

Only the P—H stretching vibration near 4.1 μ has yet been assigned (1). However, it is noted that all compounds examined containing a P(O)H link (see Table II) also absorb near 9.2, 10.2, and 18.0 μ, although most alkyl

TABLE II

P—H ASSIGNMENTS

Compounds	Ref.	Spectrum No.	Assignment in μ			
Dimethyl hydrogen phosphonate	8	31K	4.13	10.21	18.3	20.0
Diethyl hydrogen phosphonate	8	32K	4.13	10.3	18.2	19.5
Di-isopropyl hydrogen phosphonate	8	33K	4.13	10.22	18.1	18.9(sh)
Di-*n*-propyl hydrogen phosphonate		35,35K	4.13	10.22	18.2	18.9(br.sh)
Di-*n*-butyl hydrogen phosphonate	4	34K	4.13	10.22	18.1	18.9(sh)
Dimethyl hydrogen phosphonothionate		12,12K	4.18	10.5	21.1	
Diethyl hydrogen phosphonothionate		17,17K	4.18	10.6	20.6	

alkylphosphonates and many other compounds (1) also absorb near 10.2 μ, and the 9.2 band is often submerged in the P—O—(C) absorption. P(S)H compounds have the corresponding bands at 4.2, 9.2, 10.5 to 10.6, and 21 μ, as well as the doublet mentioned in section (*c*).

(*g*) *The* P—C (*Alkyl*) *Stretching Vibration*

Bellamy (1) reports that this vibration is weak, and that as it may lie in the 12–13 μ region it is doubtful whether useful correlations could be obtained. However, we have noted bands, probably connected with the P—C vibration in Me—P and Et—P compounds, which are fairly constant and which may be useful for verifying the presence of such a group. In addition to the 11 to 15 μ bands Et—P also shows an 8.15 μ band, probably corresponding to the 7.6 μ Me—P band, and most P—C compounds also have weak, broad bands in the 18–20 μ region near those assigned to P—Cl linkages (Table III).

TABLE III

P—C ASSIGNMENTS

Compounds	Ref.	Spectrum No.	Assignments in μ		
Methylphosphonyl dichloride		36		11.2	
Methylphosphonothionyl dichloride		11	11.0(s)		11.2(sh)
Dimethyl methylphosphonate	8			10.97	
Diethyl methylphosphonate	8		10.9(?)		11.1
Isopropyl methylphosphonochloridothionate		27	10.9(?)		11.15
Di-isopropyl methylphosphonate	8		10.9(?)		11.1
Di-isopropyl methylphosphonothioate		28	11.0		
Di-isopropyl dimethylmonothionopyrophosphonate		9	11.25		
Di(isopropyl methylphosphonothionyl) methylphosphonothionate		10	11.55		
Cyclohexyl methylphosphonochloridate		49	10.8(?)		11.2
Sodium cyclohexyl methylphosphonate		50		11.2	
Dibutyl methylphosphonate		37		10.85	
Ethylphosphonyl dichloride		38	8.15	13.25	13.85
Diethyl ethylphosphonate	8		8.15	13.4	14.3
Di-isopropyl ethylphosphonate	8		8.15	13.4	14.2
Di-*n*-butyl ethylphosphonate		39	8.15	13.4	14.4

(*h*) P—S—(C) *and* C—S—(P) *Stretching Vibrations*

Information available suggests that C—S—(P) gives rise to a weak band between 15.5 and 16 μ while P—S—(C) gives rise to bands near 16.5 and 17.5 μ for (O)—P—S—(C) compounds and near 18.6 and 19.4 μ for (S)P—S—(C) compounds. An additional tentative assignment of 17.7(s) μ and 19.0(sh) μ is made for trivalent P—S—(C) compounds (Table IV).

TABLE IV

P—S—(C) AND C—S—(P) ASSIGNMENTS

Compounds	Spectrum No.	Assignments in μ		
Triethyl phosphorotrithioite	*	15.7	17.7	19.0(sh)
OOS-Trimethyl phosphorothioate	*	16.5		17.6
OOS-Triethyl phosphorothioate	40,40K	15.5	16.5	17.5
SSS-Triethyl phosphorotrithioate	41,41K	15.7		17.9
OOS-Trimethyl phosphorodithioate	16K	18.8		19.7
OOS-Triethyl phosphorodithioate	23K	18.6		19.2
Triethyl phosphorotetrathioate	24K	15.6		19.1

**Although there is no doubt about the position of these bands, the compounds were not obtained sufficiently pure to warrant including their spectra.*

The 15.6 μ band is in addition to the very strong band described in section (*c*) associated with the P(S)—S— linkage and is attributed to C—S—(P) since it varies little with the substitution on the phosphorus atom. The triesters have only one very intense band beyond 16 μ, whereas the mono- and di-esters have two, the one at shorter wavelengths being the weaker. These bands are attributed to the P—S—(C) link.

(*i*) P—S—(H) *Stretching Vibrations*

Little has been reported in the literature concerning the position of absorption due to this vibration. Our results tend to indicate that this absorption is close to that due to P—S—(C) but at slightly longer wavelengths. When P(S) groups replace P(O) groups the band shifts to longer wavelengths (Table V).

It will be noted that the band positions in the spectrum of the ion differ little from those of the acid in the one case studied, but the bands are sharper and the relative intensities are reversed.

TABLE V

P—S—(H) ASSIGNMENTS

Compounds	Spectrum No.	Assignments in μ	
Dimethyl phosphorodithioic acid	13K	19.0	20.3
Diethyl phosphorothioic acid	19K	15.4	16.2
Diethyl phosphorothioic acid, triethylamine salt	42K	15.4	16.3
Diethyl phosphorodithioic acid	18K	18.5	19.7

(*j*) P—S—(P) *Stretching Vibrations*

By analogy with the behavior of P—O—(C) and P—O—(P) bands, the P—S—(P) would be expected to absorb at somewhat longer wavelengths than

the corresponding P—S—(C) bands. None of the esters of phosphorus monothiopyroacids prepared in this work show any bands in the 12–26 μ region, except a few containing P—S—(C) impurities. However, one compound containing P(S)—S—P(S) has been prepared and examined. Attempts to synthesize other compounds containing P(S)—S—P(S) and P(O)—S—P(S) seem to have been partially successful, but all attempts to obtain them in a pure state have resulted in the decomposition of the small amount present. *SS*-Di-(diethyl phosphorothionyl)-*O*-ethyl phosphorotrithioate (spectrum No. 25K) has bands at 20.0 μ and 21.7 μ, while an impure sample of what was probably *OOOO*-tetraethyl trithiopyrophosphate had a band at 20.5 μ not present in the starting materials.

(*k*) *The* P—Cl *Stretching Vibration*

Daasch and Smith (4) have reported that P—Cl bands occur from 19 to 23 μ, usually giving a doublet when two or more chlorines are present and a single band when one chlorine is present. Our results are summarized in Table VI.

TABLE VI

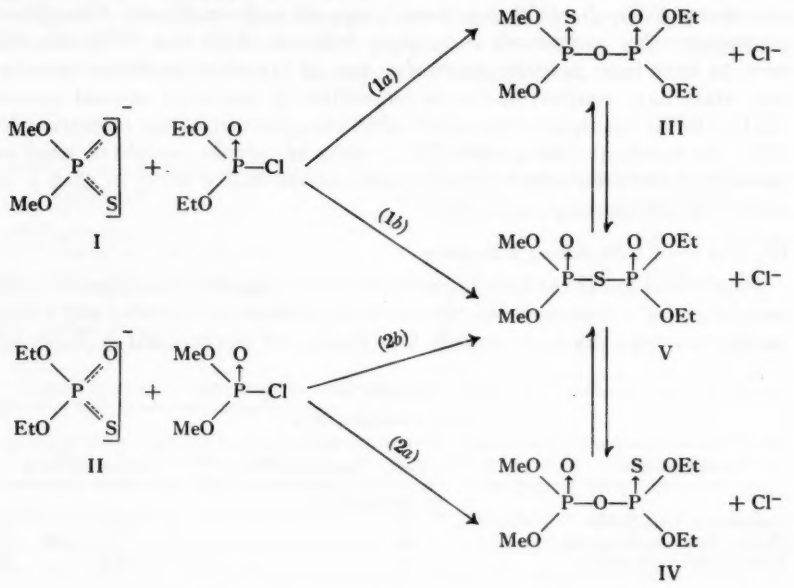
P—Cl ASSIGNMENTS

Compounds	Ref.	Spectrum No.	Assignment in μ		
(i) Trivalent P					
Phosphorus trichloride	4		19.6		20.5
Phenyl dichlorophosphine	4			20	
Ethyl dichlorophosphine	4		19.9		20.5
(ii) O ↑ P—Cl					
Phosphorus oxychloride	4		17.2		20.6
Methylphosphonyl dichloride		36K	18.3		20.2
Ethylphosphonyl dichloride		38K	17.6	18.5	20.0
Dimethyl phosphorochloridate		43K	16.7		18.1
Diethyl phosphorochloridate		44K	16.7		18.1
Di-*n*-propyl phosphorochloridate		45K	16.7		18.0
Di-isopropyl phosphorochloridate		46K	16.7		18.0
(iii) S ↑ P—Cl					
Phosphorothionyl trichloride	4		18.6		23.1
Methylphosphonothionyl dichloride		11K	19.4		22.2
Methyl phosphorodichloridothionate		14K 18(?)	18.8	21	22.1
Ethyl phosphorodichloridothionate		20K 18.1(?)	18.9(?)	20.5	21.3
Dimethyl phosphorochloridothionate		15K	19.0		20.5
Diethyl phosphorochloridothionate		21K	18.7		20.1
Di-*n*-propyl phosphorochloridothionate		26K	18.5		19.7
Di-isopropyl phosphorochloridothionate		29K	18.5		19.7
Di-*n*-butyl phosphorochloridothionate		30K	18.5(sh)		19.3

Although there is considerable variation in each group depending on the number of halogen substituents and whether P—C links are present, P(O)Cl compounds usually absorb in the 17–18 μ region, P(S)Cl compounds in the 18–20 μ region, and trivalent phosphorus compounds close to 20 μ.

Application

To establish the usefulness of these correlations, reactions (1) and (2) were carried out and the products examined.



When ions I and II are treated with alkyl halides, reaction takes place almost exclusively at the sulphur atom. If this occurred when dialkyl phosphorochloridates were used, both reactions would yield the same P—S—P isomer V. Since previous experience has shown that the final product of this type of reaction is a thiono isomer, V if formed would be expected to rearrange to III, IV, or a mixture of the two. In either case the same product or mixture should result. If, however, reaction took place only at the oxygen atom, reaction (1) should give only III, and reaction (2) only IV, unless interconversion of III and IV via V if possible. Infrared absorption would be the only physical property which would readily distinguish between these possibilities.

On the basis of the correlations given earlier, some of the features expected in the spectra of III and IV were predicted. Both compounds would be expected to have a P → S band near 12 μ and a P—O—P band near 10.5 μ. The main differences were expected in the CH and alkyl group deformation.

Structure III would be expected to have a MeO band near 6.85 μ, superimposed on the EtO—P(O) bands at 6.75, 6.92, 7.17, and 7.3 μ, while structure IV would lack the 7.3 μ band. The sharp characteristic C—O—(P) bands of MeO and EtO should both be present, at approximately 8.45 μ and 8.58 μ for structure III, and 8.41 and 8.60 μ for structure IV, qualitatively a greater separation for IV. Owing to the breadth and intensity of the P—O—(C) bands, differences would be less noticeable, but III should exhibit intense absorption in the 9.65 μ to 9.8 μ region and have a second band near 10.2 μ, while IV

TABLE VII

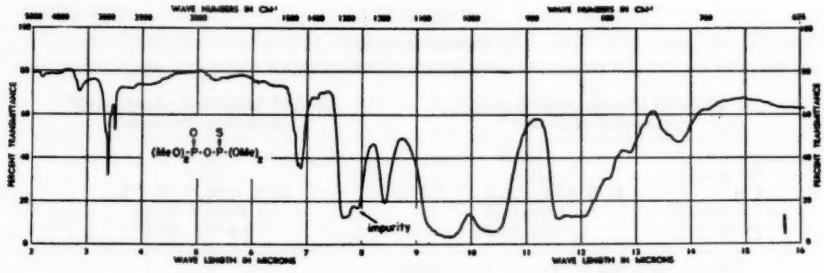
OBSERVED BANDS

	III (Diethyl phosphoryl) dimethyl phosphorothionate	IV Diethyl (dimethyl phosphoryl) phosphorothionate
P → S	12.05	12.05
P—O—P	10.5	10.5*
CH	6.75, 6.85, 6.9, 7.17, 7.3	6.78, 6.85, 6.92, 7.2
C—O—(P)	8.45, 8.55	8.42, 8.59
P—O—(C)	9.62, 10.25	9.4–9.8, 10.4*

**P—O—(C) and P—O—(P) not resolved.*

INDEX TO SPECTRA

	Spectrum No.
Cyclohexyl methylphosphonochloridate	49
Di-*n*-butyl ethylphosphonate	39
Di-*n*-butyl hydrogen phosphonate	34
Di-*n*-butyl methylphosphonate	37
Di-*n*-butyl phosphorochloridothionate	30
SS-Di(diethyl phosphorothionyl)-*O*-ethyl phosphorotrithioate	25
Diethyl (dimethyl phosphoryl) phosphorothionate	48
Diethyl hydrogen phosphonate	32
Diethyl hydrogen phosphonothionate	17
Diethyl phosphorochloridate	44
Diethyl phosphorochloridothionate	21
Diethyl phosphorodithioic acid	18
Diethyl phosphorothioic acid	19
Diethyl phosphorothioic acid, triethylamine salt	42
(Diethyl phosphoryl) dimethyl phosphorothionate	47
Di-isopropyl dimethylmonothionopyrophosphonate	9
Di-isopropyl hydrogen phosphonate	33
Di-isopropyl methylphosphonothionate	28
Di(isopropyl methylphosphonothionyl) methylphosphonothionate	10
Di-isopropyl phosphorochloridate	46
Di-isopropyl phosphorochloridothionate	29
Dimethyl hydrogen phosphonate	31
Dimethyl hydrogen phosphonothionate	12
Dimethyl phosphorochloridate	43
Dimethyl phosphorochloridothionate	15
Dimethyl phosphorodithioic acid	13
Di-*n*-propyl hydrogen phosphonate	35
Di-*n*-propyl phosphorochloridate	45
Di-*n*-propyl phosphorochloridothionate	26
Ethylphosphonyl dichloride	38
Ethyl phosphorodichloridothionate	20
Isopropyl methylphosphonochloridothionate	27
Methylphosphonothionyl dichloride	11
Methylphosphonyl dichloride	36
Methyl phosphorodichloridothionate	14
Sodium cyclohexyl methylphosphonate	50
Tetra-*n*-butyl monothionopyrophosphate	8
Tetraethyl dithionopyrophosphate	4
Tetraethyl monothionopyrophosphate	3
Tetraethyl pyrophosphate	2
Tetraisopropyl monothionopyrophosphate	7
Tetramethyl monothionopyrophosphate	1
Tetra-*n*-propyl monothionopyrophosphate	6
Tetra-*n*-propyl pyrophosphate	5
OOS-Triethyl phosphorodithioate	23
Triethyl phosphorotetrathioate	24
OOS-Triethyl phosphorothioate	40
Triethyl phosphorothionate	22
SSS-Triethyl phosphorotrithioate	41
OOS-Trimethyl phosphorodithioate	16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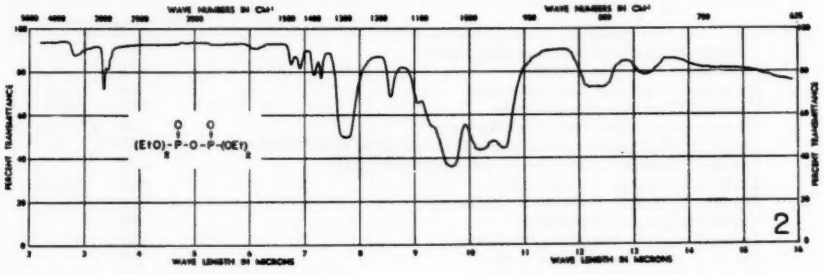
impurity
WAVE LENGTH IN MICRONS
1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PERCENT TRANSMITTANCE
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WAVE LENGTH IN MICRONS
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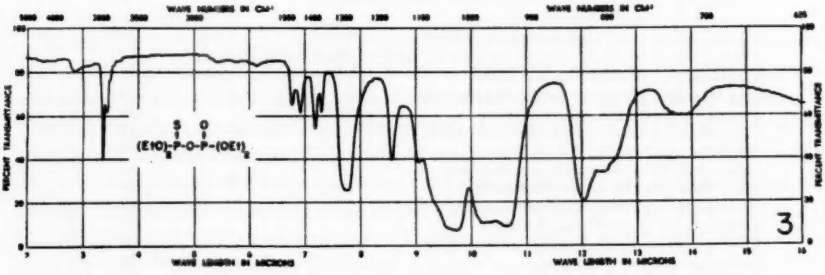
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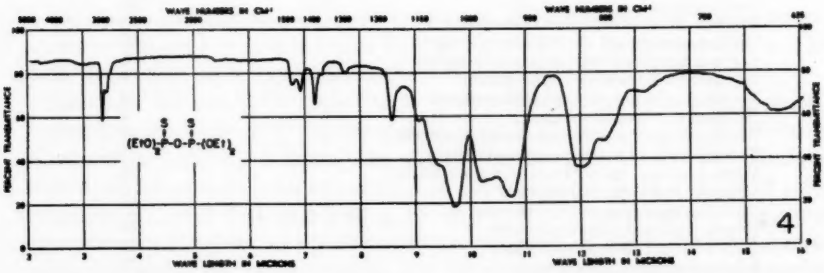
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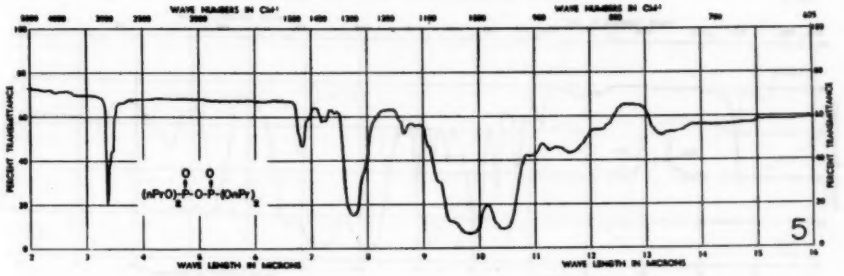
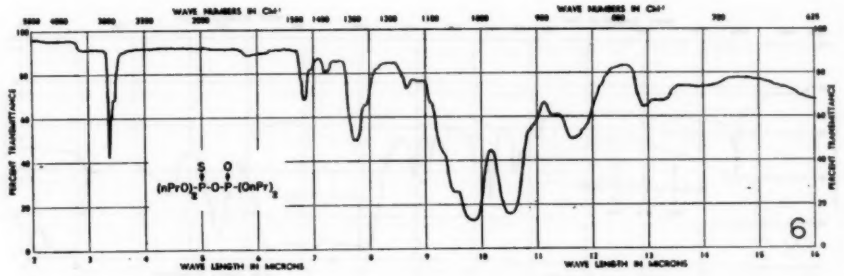
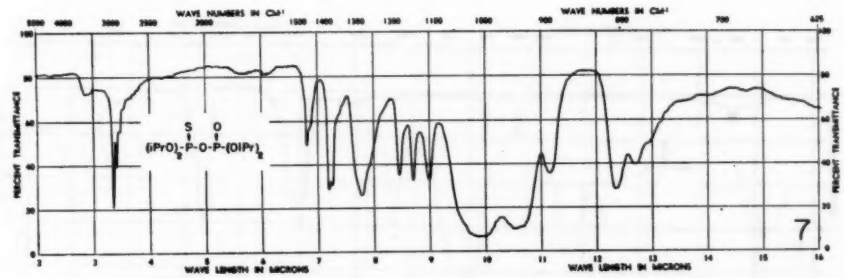
PERCENT TRANSMITTANCE
(EtO)₂-P-O-P-(OEt)₂
WAVE LENGTH IN MICRONS
4


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
O O
(nPrO)2-P-O-P-(OnPr)2
5


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
S O
(nPrO)2-P-O-P-(OnPr)2
6


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
S O
(iPrO)2-P-O-P-(OiPr)2
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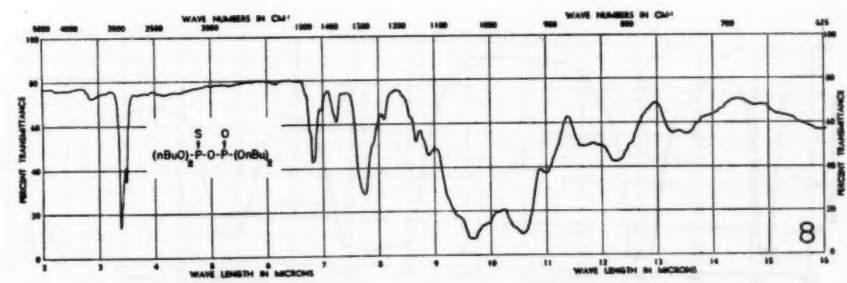
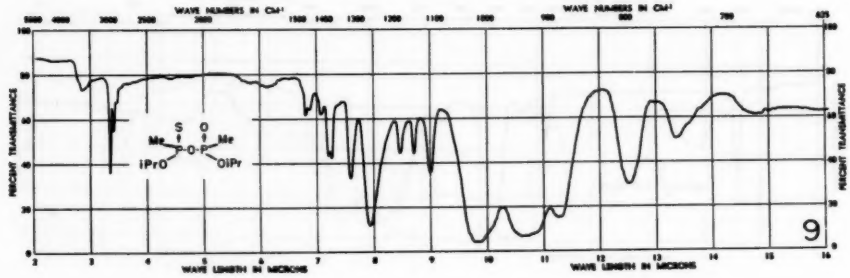
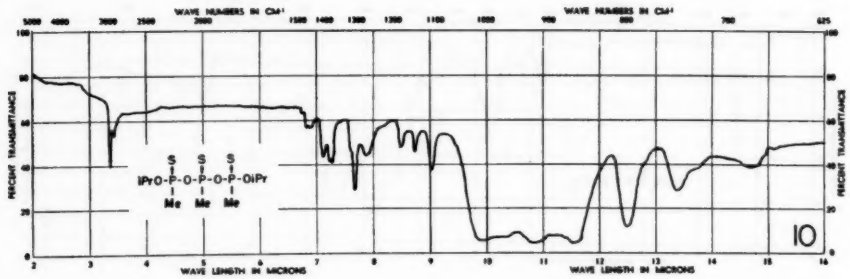
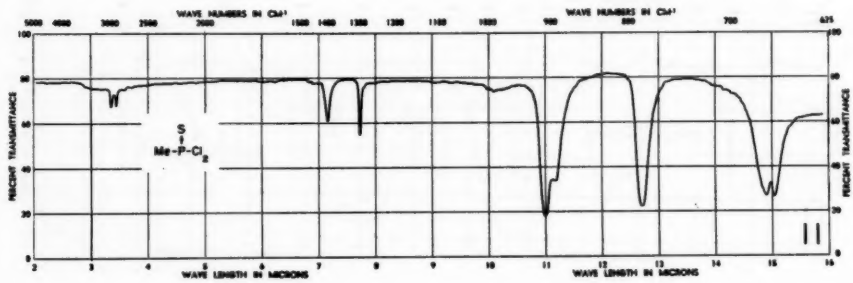
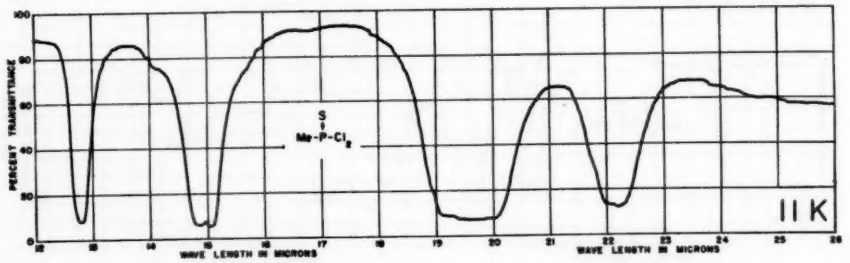
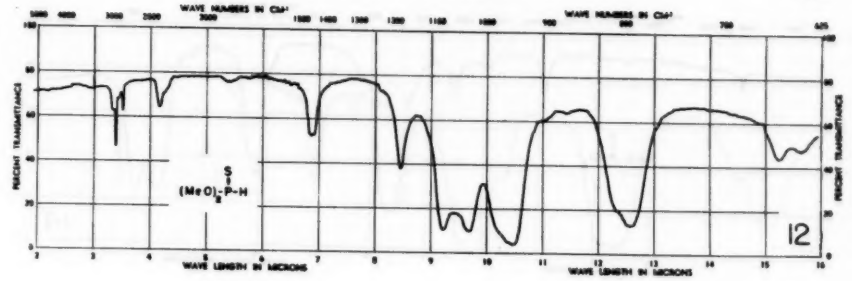

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
S O
(nBuO)2-P-O-P-(OnBu)2
8

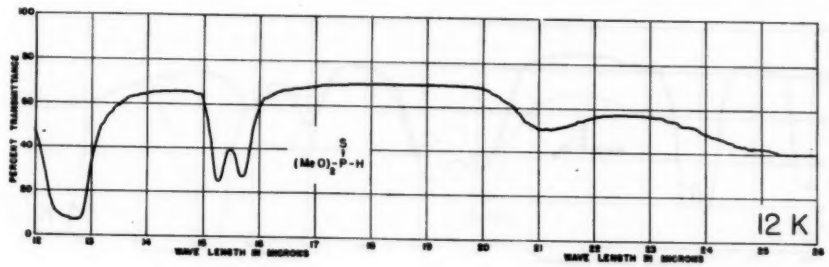

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
Me
S
P-O-P
Me
iPrO
OiPy
9

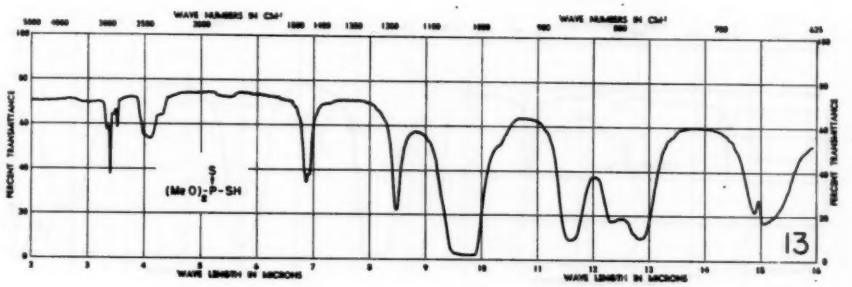

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
iPrO-P-O-P-O-P-OiPy
Me Me Me
10

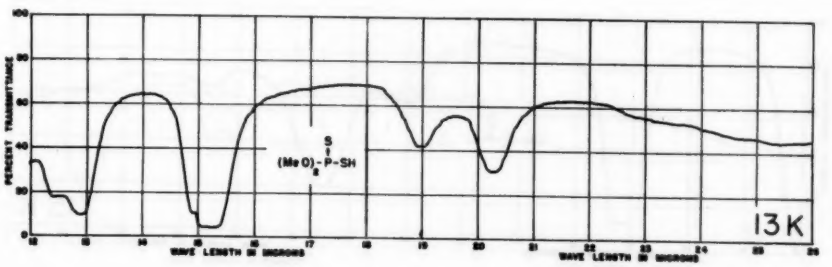

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
Me-P-Cl2
11

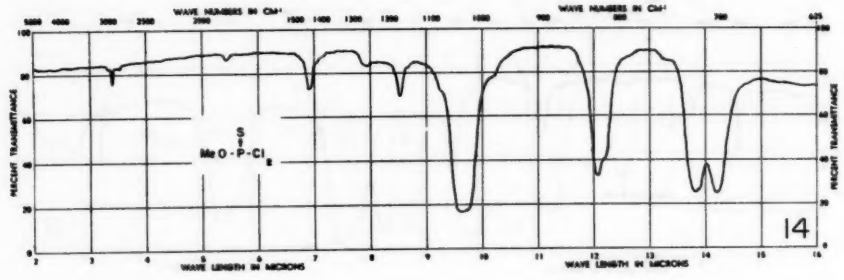

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
Me-P-Cl2
11K

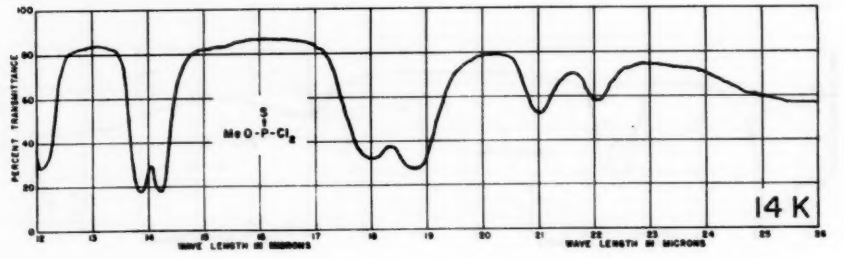

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(MeO)₂P-H
12
WAVE LENGTH IN MICRONS

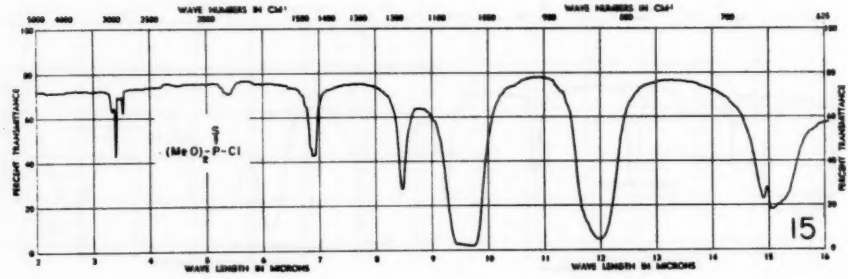

PERCENT TRANSMITTANCE
(MeO)₂P-H
12 K
WAVE LENGTH IN MICRONS

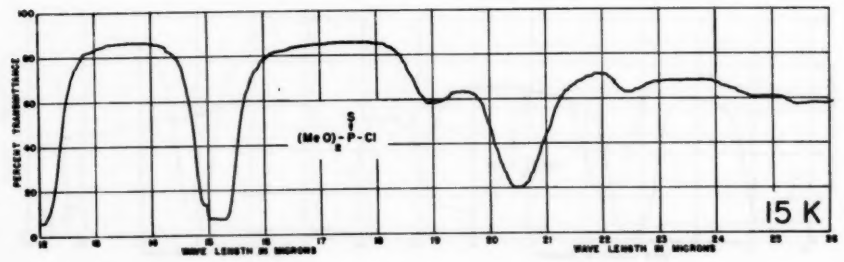

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(MeO)₂P-SH
13
WAVE LENGTH IN MICRONS

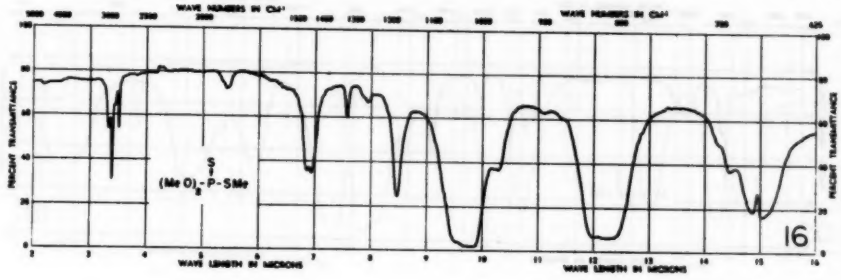

PERCENT TRANSMITTANCE
(MeO)₂P-SH
13 K
WAVE LENGTH IN MICRONS

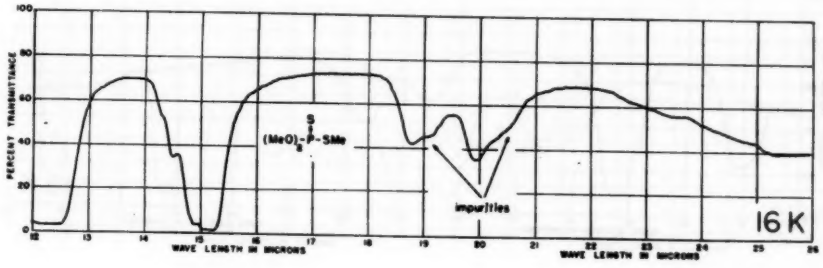

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
MeO-P-Cl₂
O
14
WAVE LENGTH IN MICRONS

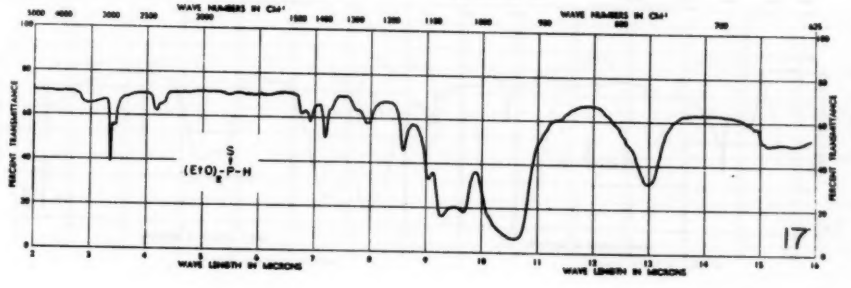

PERCENT TRANSMITTANCE
MeO-P-Cl₂
O
14 K
WAVE LENGTH IN MICRONS

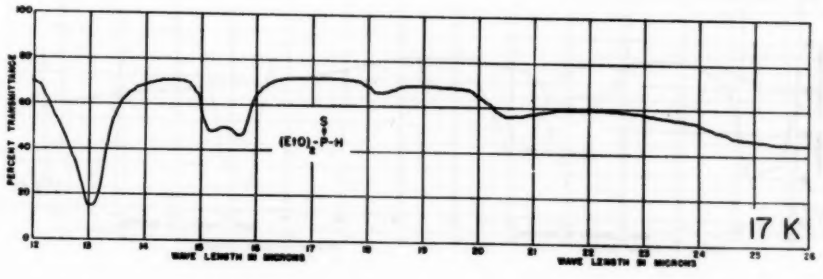

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(MeO)₂-P-Cl
O
15
WAVE LENGTH IN MICRONS

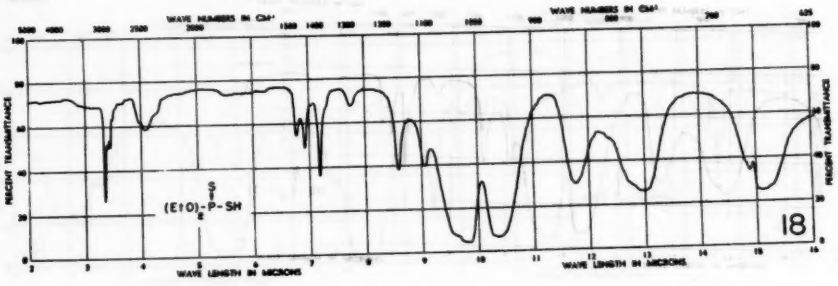

PERCENT TRANSMITTANCE
(MeO)₂-P-Cl
O
15 K
WAVE LENGTH IN MICRONS

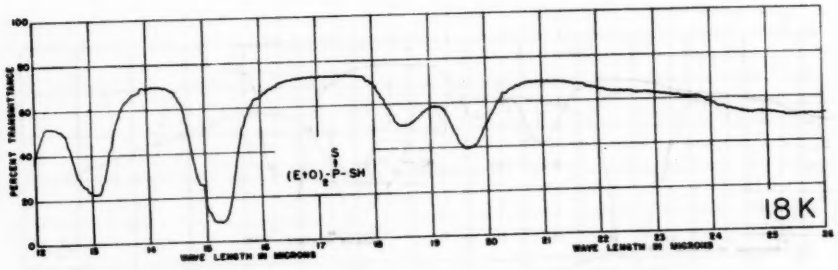

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(MeO)₂-P-SMe
16
WAVE LENGTH IN MICRONS

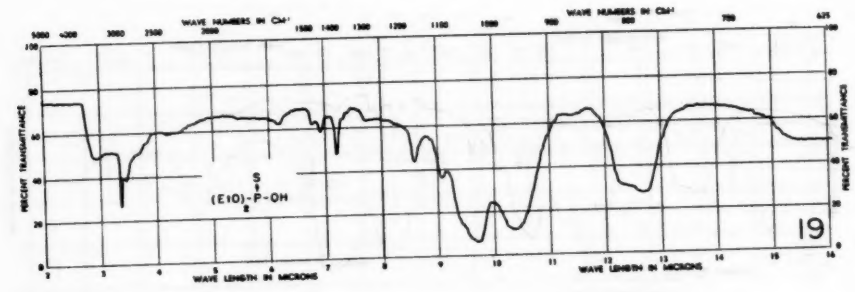

PERCENT TRANSMITTANCE
(MeO)₂-P-SMe
impurities
16 K
WAVE LENGTH IN MICRONS

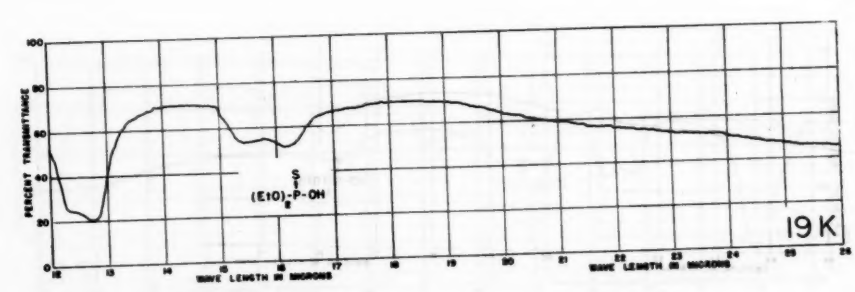

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(EtO)₂-P-H
17
WAVE LENGTH IN MICRONS

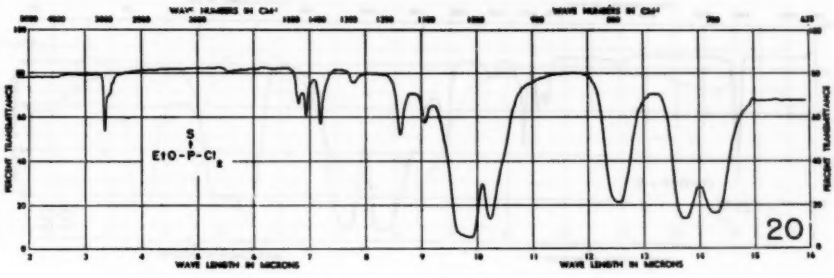

PERCENT TRANSMITTANCE
(EtO)₂-P-H
17 K
WAVE LENGTH IN MICRONS

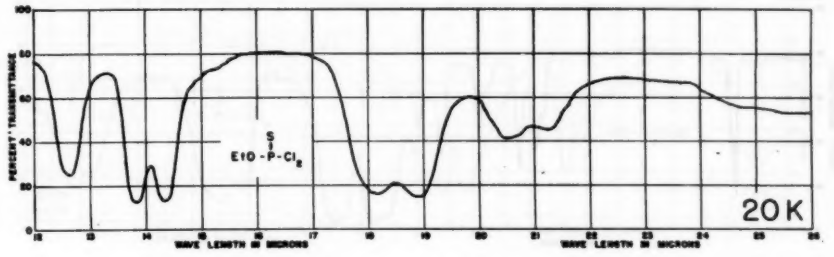

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(E10)-P-SH
18

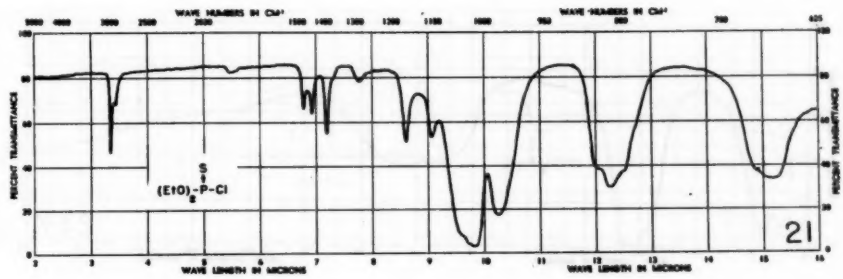

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(E10)-P-SH
18 K

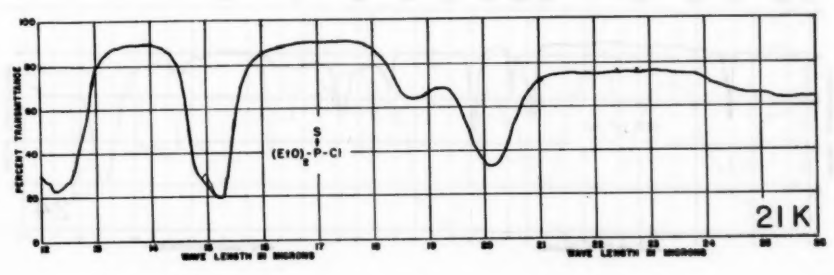

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(E10)-P-OH
19

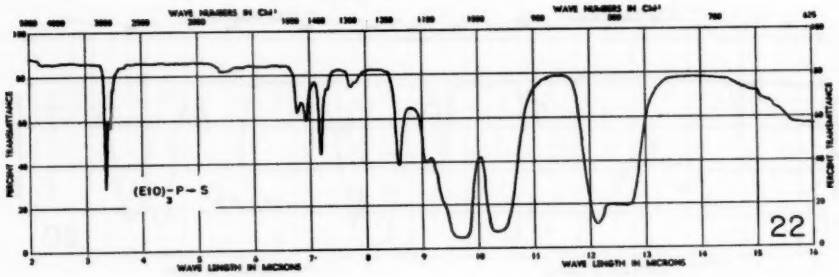

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(E10)-P-OH
19 K

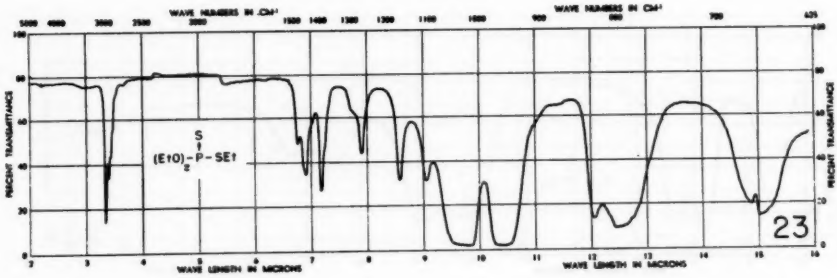

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
S
E10-P-Cl2
20

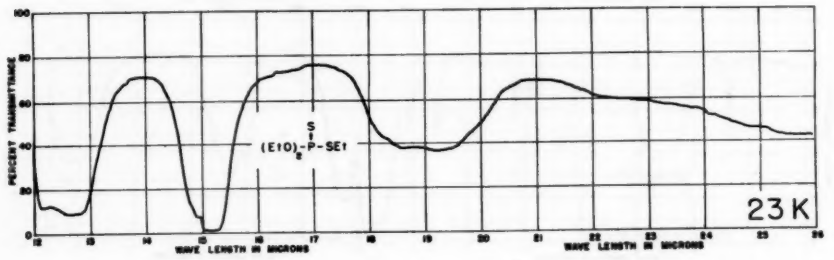

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
S
E10-P-Cl2
20K

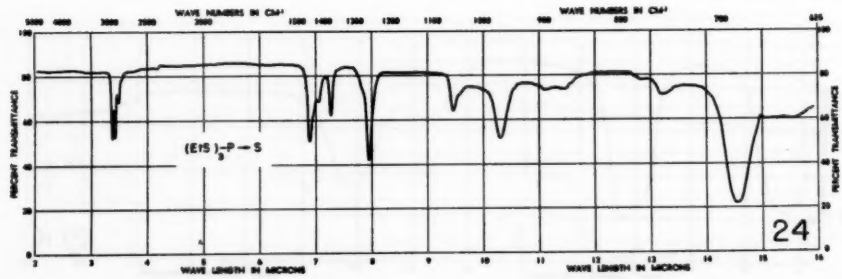

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(E10)2-P-Cl
21

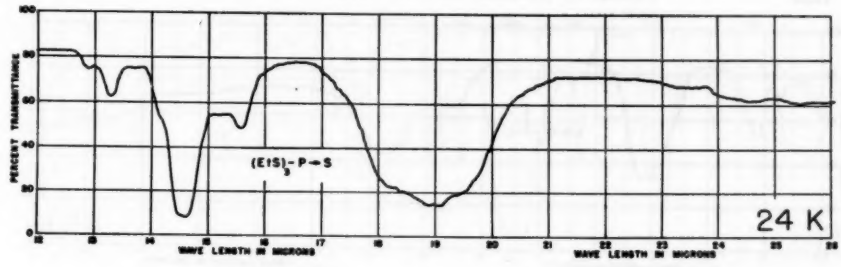

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(E10)2-P-Cl
21K

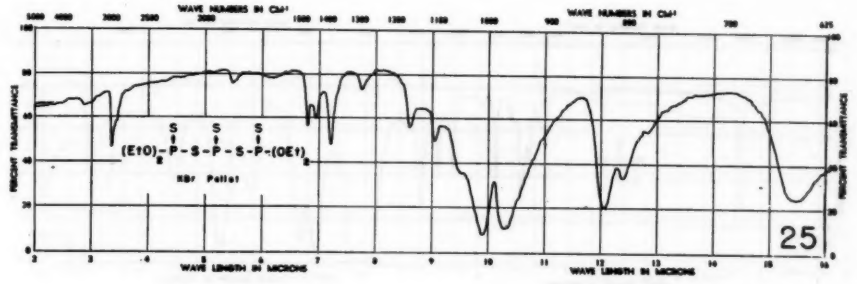

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(E10)$_3$P—S
22
WAVE LENGTH IN MICRONS

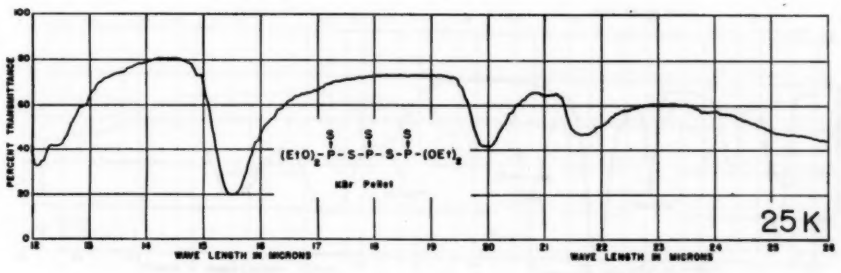

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(E10)$_2$P(S)SEt
23
WAVE LENGTH IN MICRONS

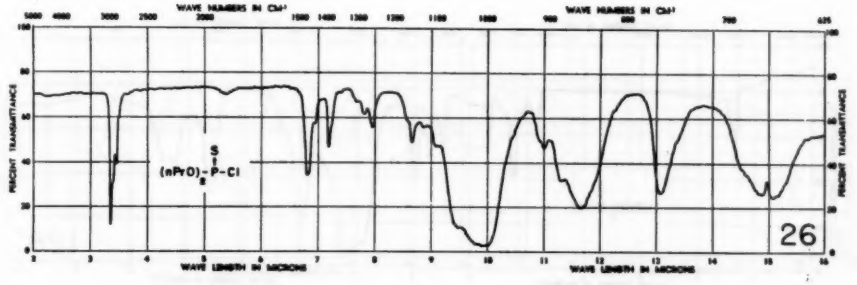

PERCENT TRANSMITTANCE
(E10)$_2$P(S)SEt
23 K
WAVE LENGTH IN MICRONS

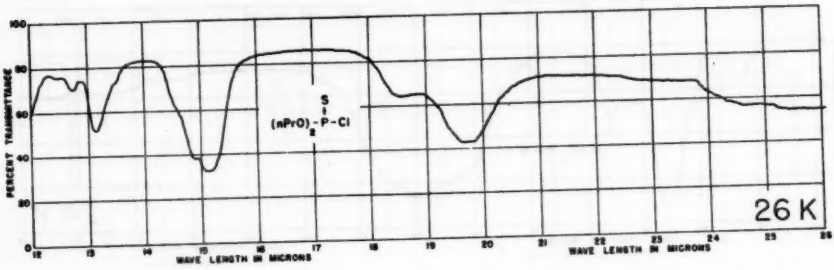

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(E15)$_3$P—S
24
WAVE LENGTH IN MICRONS

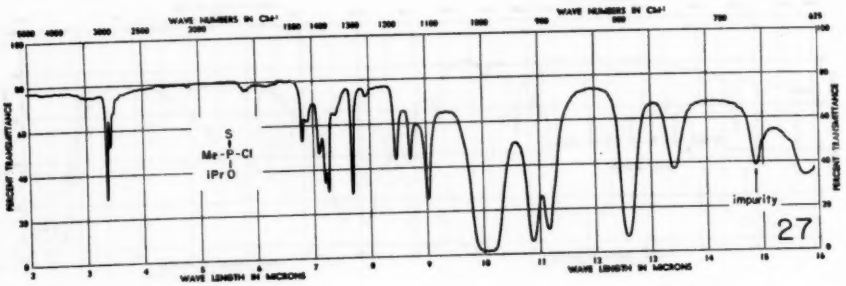

PERCENT TRANSMITTANCE
(EtS)$_3$-P→S
24 K
WAVE LENGTH IN MICRONS

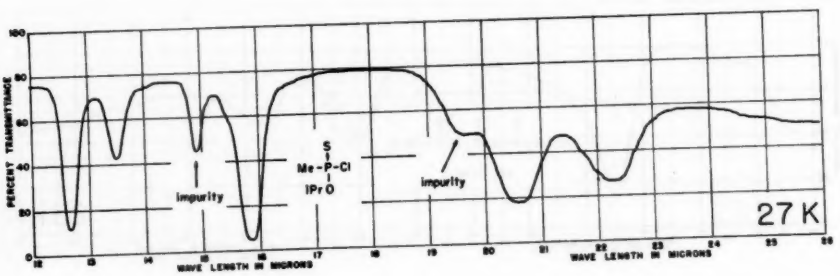

WAVE NUMBERS IN CM^{-1}
PERCENT TRANSMITTANCE
(EtO)$_2$-P-S-P-S-P-(OEt)$_2$
KBr Pellet
25
WAVE LENGTH IN MICRONS

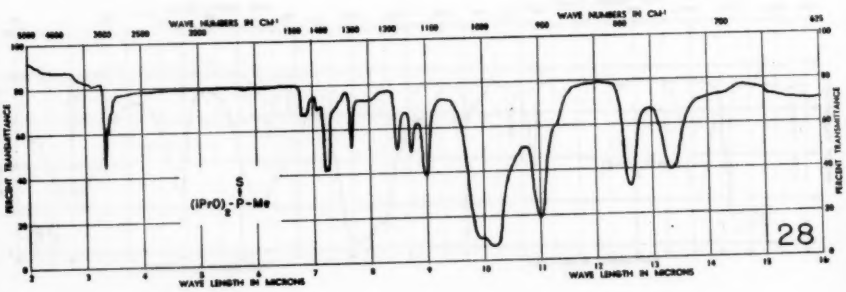

PERCENT TRANSMITTANCE
(EtO)$_2$-P-S-P-S-P-(OEt)$_2$
KBr Pellet
25K
WAVE LENGTH IN MICRONS

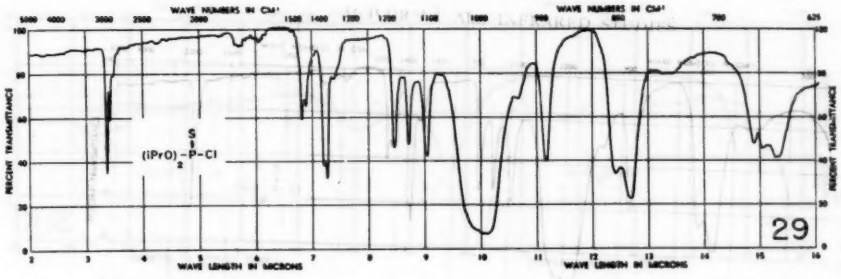

WAVE NUMBERS IN CM^{-1}
PERCENT TRANSMITTANCE
(nPrO)$_2$-P-Cl
26
WAVE LENGTH IN MICRONS

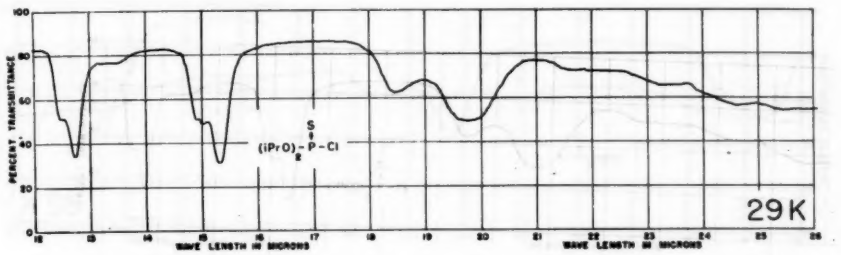

PERCENT TRANSMITTANCE
(nPrO)2-P-Cl
S
26 K
WAVE LENGTH IN MICRONS

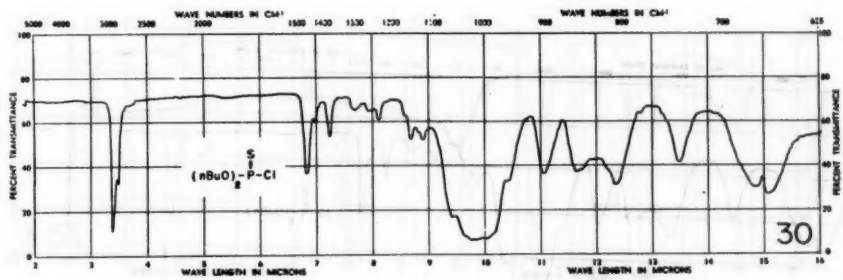

WAVE NUMBERS IN CM-1
PERCENT TRANSMITTANCE
Me-P-Cl
IPrO
S
impurity
27
WAVE LENGTH IN MICRONS

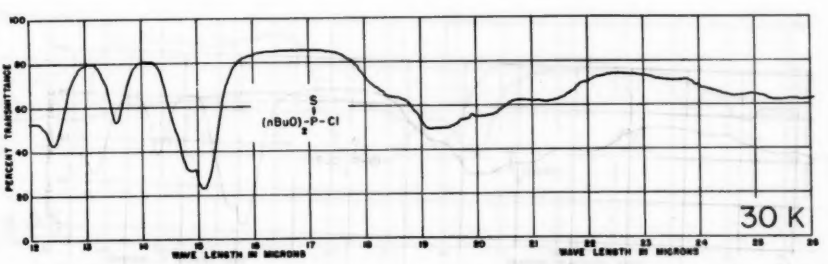

PERCENT TRANSMITTANCE
impurity
Me-P-Cl
IPrO
S
impurity
27 K
WAVE LENGTH IN MICRONS

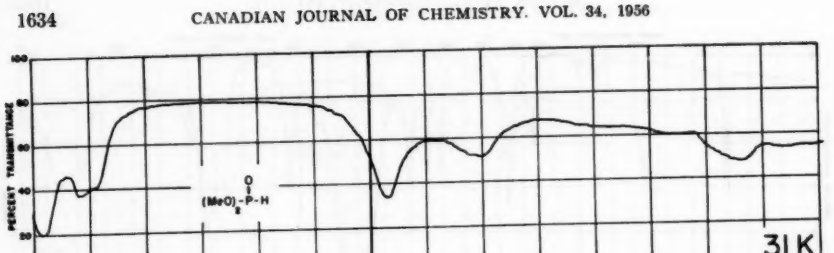

WAVE NUMBERS IN CM-1
PERCENT TRANSMITTANCE
(IPrO)2-P-Me
S
28
WAVE LENGTH IN MICRONS

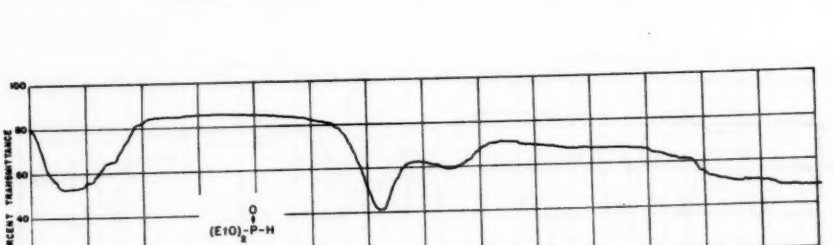

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(iPrO)2-P-Cl
S
29

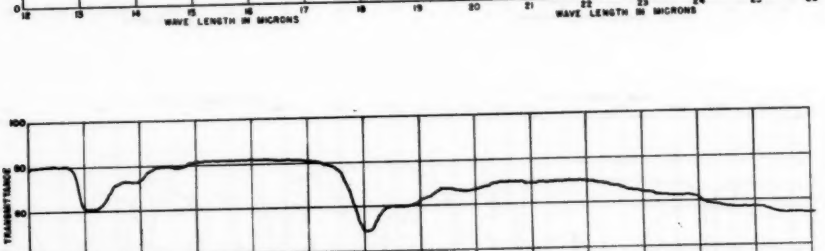

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(iPrO)2-P-Cl
S
29K

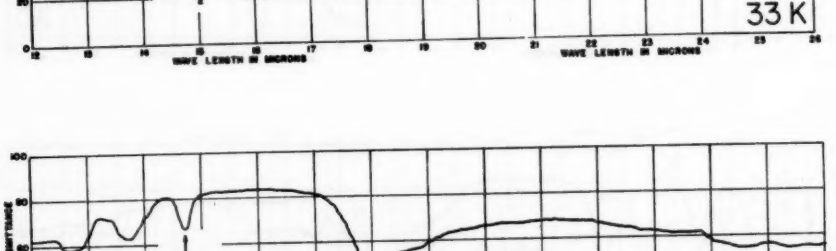

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(nBuO)2-P-Cl
S
30

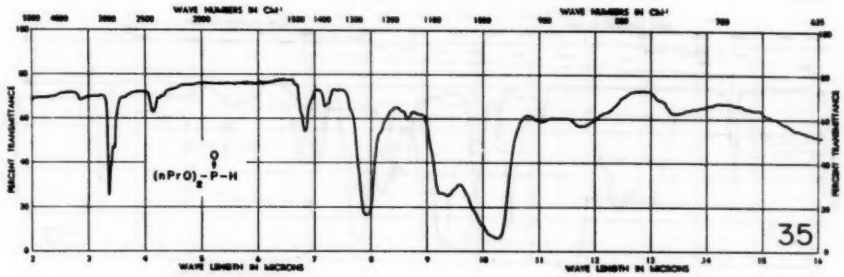

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(nBuO)2-P-Cl
S
30 K

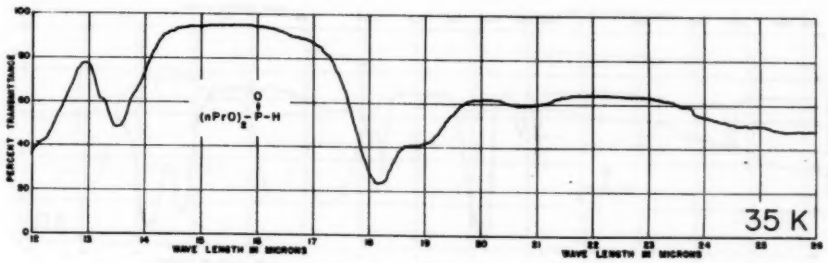

PERCENT TRANSMITTANCE
(MeO)2-P-H
31 K
WAVE LENGTH IN MICRONS

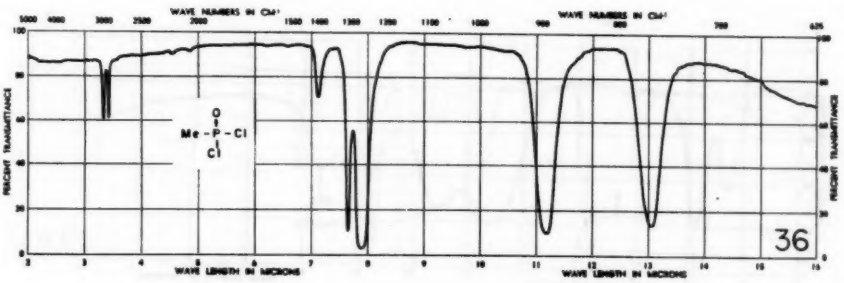

PERCENT TRANSMITTANCE
(EtO)2-P-H
32 K
WAVE LENGTH IN MICRONS

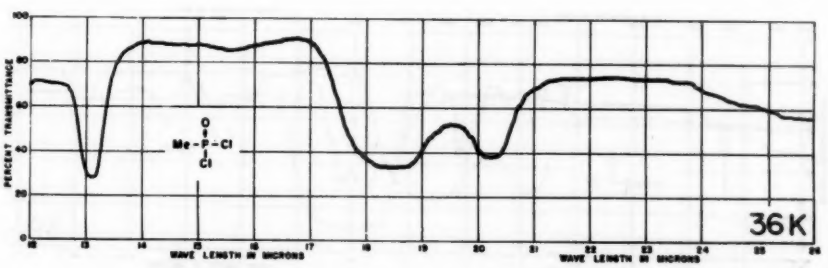

PERCENT TRANSMITTANCE
(iPrO)2-P-H
33 K
WAVE LENGTH IN MICRONS

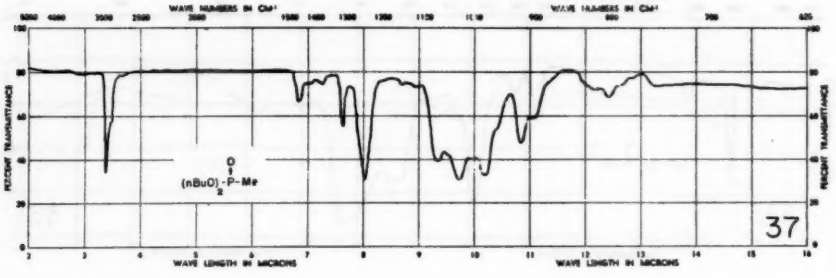

PERCENT TRANSMITTANCE
C6H6 Impurity
(nBuO)2-P-H
34 K
WAVE LENGTH IN MICRONS

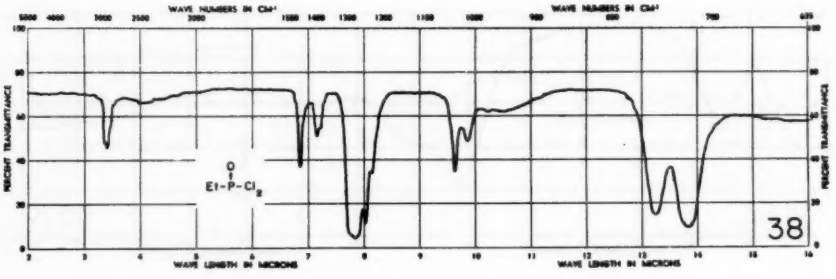

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(nPrO)$_2$-P-H
35

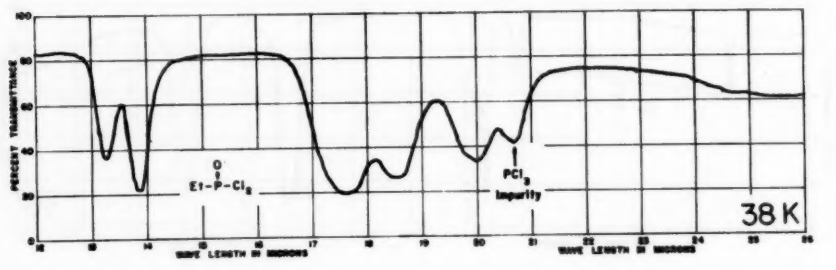

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
(nPrO)$_2$-P-H
35 K

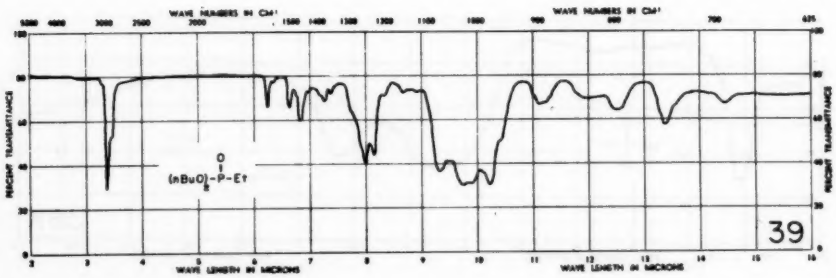

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
Me-P-Cl
Cl
36

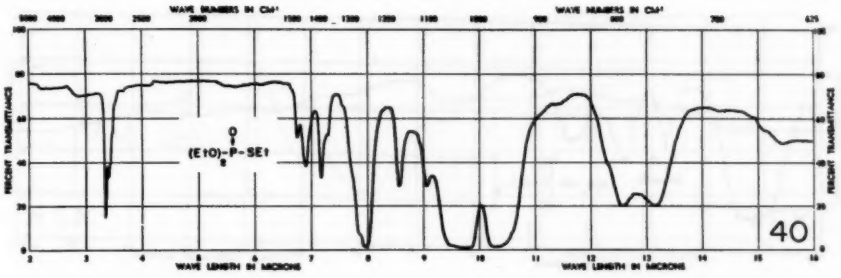

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
Me-P-Cl
Cl
36K

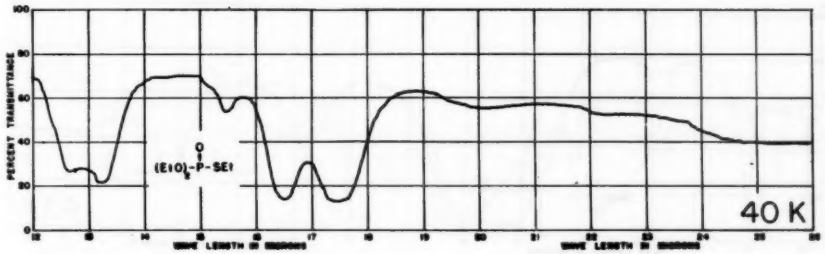

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(nBuO)₂-P-Me
37
WAVE LENGTH IN MICRONS

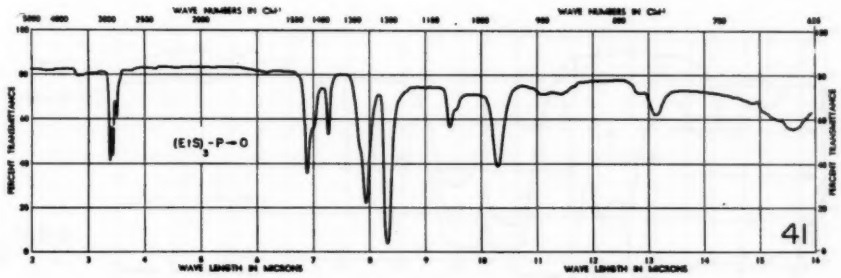

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
Et-P-Cl₂
38
WAVE LENGTH IN MICRONS

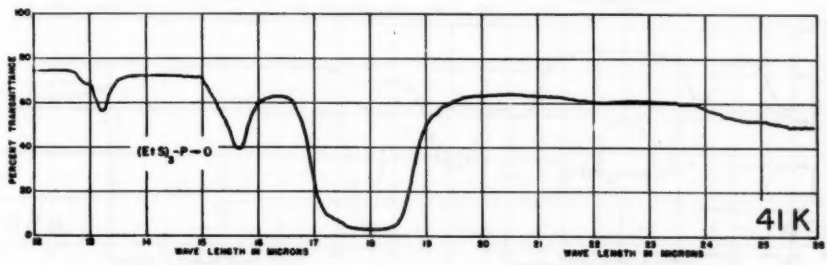

PERCENT TRANSMITTANCE
Et-P-Cl₂
PCl₃
Impurity
38 K
WAVE LENGTH IN MICRONS

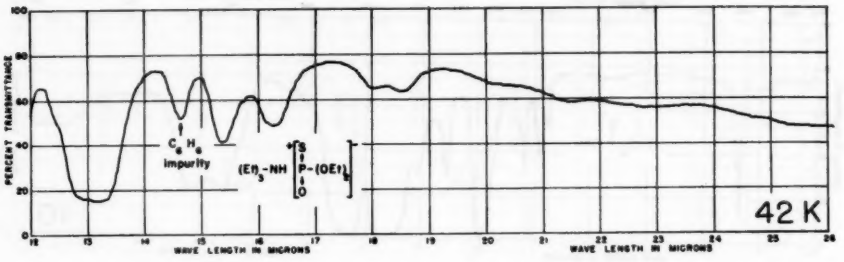

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
(nBuO)₂-P-Et
39
WAVE LENGTH IN MICRONS

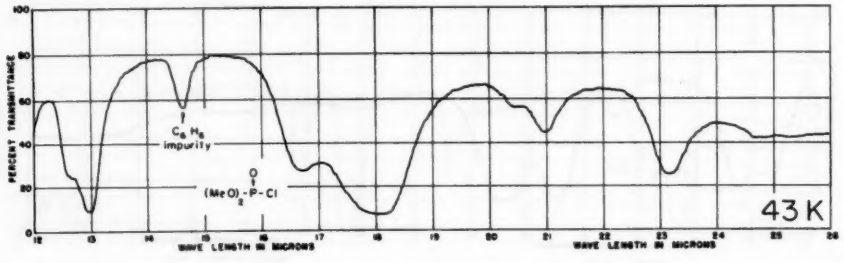

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
40

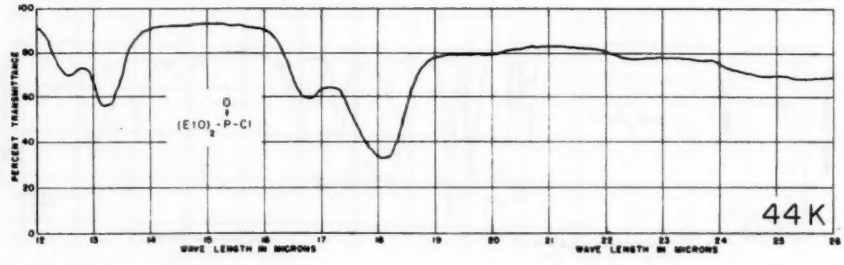

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
40 K

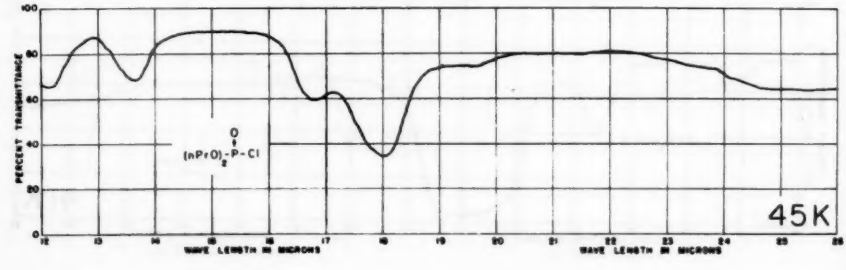

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
41

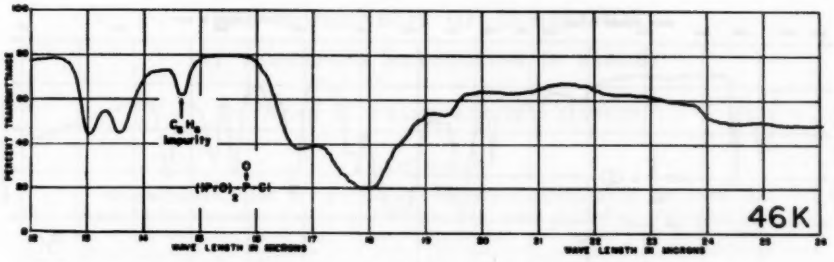

PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
41 K

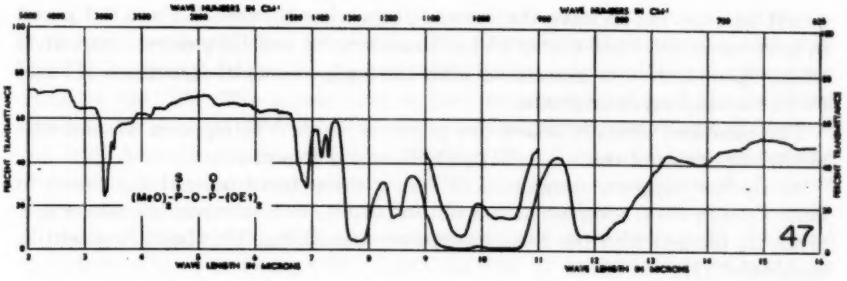

PERCENT TRANSMITTANCE
C_6H_6 impurity
$(Et)_3$-NH $\left[\begin{matrix}S\\|\\P\text{-}(OEt)_2\\|\\O\end{matrix}\right]_2$
42 K
WAVE LENGTH IN MICRONS

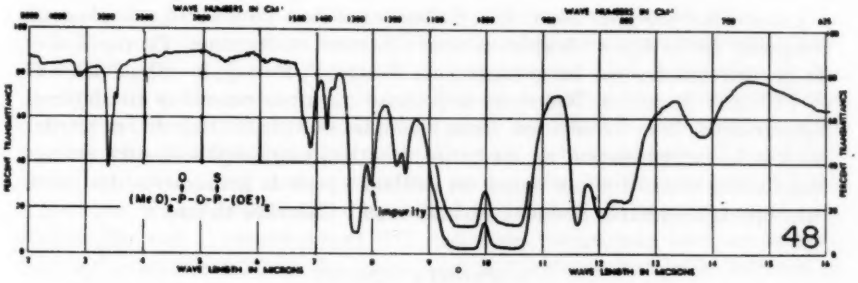

PERCENT TRANSMITTANCE
C_6H_6 impurity
$(MeO)_2$-P-Cl
43 K
WAVE LENGTH IN MICRONS

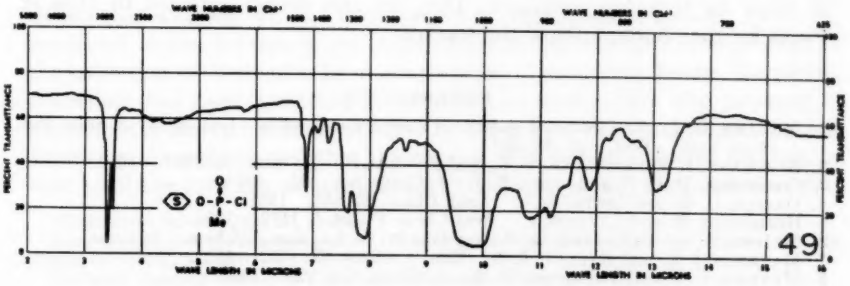

PERCENT TRANSMITTANCE
$(EtO)_2$-P-Cl
44 K
WAVE LENGTH IN MICRONS

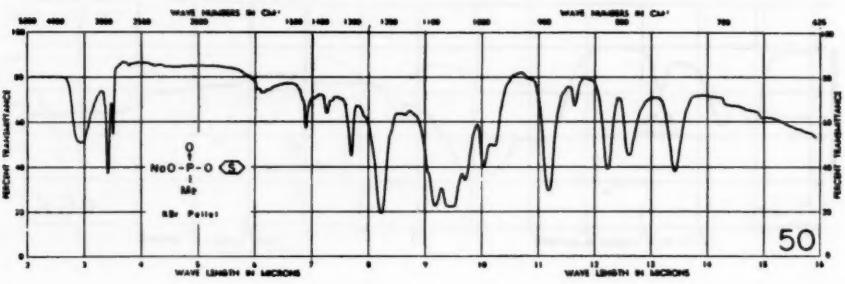

PERCENT TRANSMITTANCE
$(nPrO)_2$-P-Cl
45 K
WAVE LENGTH IN MICRONS


PERCENT TRANSMITTANCE
C_6H_6 Impurity
$(iPrO)_2$-P-Cl
O
46K
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
$(MeO)_2$-P-O-P-$(OEt)_2$
S O
47
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
$(MeO)_2$-P-O-P-$(OEt)_2$
O S
Impurity
48
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
O-P-Cl
Me
49
WAVE LENGTH IN MICRONS



would be expected to have the intense absorption between 9.5 and 9.8 μ and to have its second band nearer 10.4 μ. Reactions (1) and (2) yielded compounds whose spectra were in agreement with the assignments of structures III and IV to the respective products.

The positions actually found are given in Table VII (spectra 47 and 48). Small impurities of the type $(RO)_2$ POSR are still evident.

As further support, compound IV has a sharp band near 11.6 μ found in most $(MeO)_2$ P(O) compounds but not in $(MeO)_2$ P(S) compounds, where it is probably merged with the P(S) absorption near 12.0 μ. This band is absent in compound III.

RÉSUMÉ

Les attributions pour les bandes d'absorption dans l'infra-rouge de plusieurs composés aliphatiques phosphorés sont résumées et étendues. En particulier, les bandes données par les groupements P—O—P, P → S, P—SH, PSR, PH, et PCl sont discutées. Nous avons proposé quelques nouvelles attributions, surtout entre 12 et 24 microns. Deux examples de l'application de ces attributions à la détermination de structure des thiopyrophosphates sont donnés. Nous avons démontré que toutes les méthodes pour la préparation des monothionopyrophosphates donnent exclusivement l'isomère thiono.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Messrs. R. A. Hinge and A. Grey for technical assistance. They are also deeply indebted to Miss R. Parks for the photographs of the spectra.

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THE BIOGENESIS OF ALKALOIDS

XVI. HORDENINE METABOLISM IN BARLEY[1]

By Arlen W. Frank[2] and Léo Marion

ABSTRACT

Hordenine-α-C^{14} fed to sprouting barley was metabolized in the roots. Exhaustive fractionation of extracts from the dried roots yielded several substances of which only the hordenine, N-methyltyramine, and lignin were radioactive. Phenylalanine and tyrosine were inert. The results show that the methylation of tyramine to hordenine is at least partly reversible, but that the hordenine does not revert to tyrosine or phenylalanine. They also indicate that hordenine or N-methyltyramine become incorporated into the lignin.

It has been established previously that both N-methyltyramine and hordenine, occurring in the roots of germinating barley, originate from the precursor tyrosine (14, 15). The amino acid is first decarboxylated and the resulting tyramine is methylated via methionine to N-methyltyramine and to hordenine (12). According to Raoul (19) and others (6, 27), the alkaloids are present in barley during only approximately 30 days. The concentration of alkaloids starts at zero, since none are present in the seed, reaches a maximum at about 11 days of growth, and gradually decreases to zero after one month. This can be interpreted as meaning that during the first 11 days the rate of synthesis of the alkaloids is greater than the rate at which it is used up, whereas after that period it is degraded at a faster rate than it is formed. It was of interest, therefore, to investigate the transformation of hordenine in the plant.

It has been suggested by Raoul (19) on the basis of *in vitro* experiments performed under supposedly physiological conditions that hordenine is demethylated in the plant to tyramine. The same author also investigated the recarboxylation of the demethylated product, but failed to find proper *in vitro* methods under which this step could take place. It has also been assumed (12) that hordenine could undergo further methylation to the quaternary base candicine, which occurs together with hordenine in *Trichocereus candicans* Gillis (20) and *T. lamprochlorus* (16), but these suggestions have never been verified experimentally in the plant, and no candicine has been detected in barley.

Investigations of the behavior of hordenine toward isolated enzymes have shown that whereas tyrosine is converted by tyrosinase to melanin (4, 9, 19) hordenine is not, because of the substitution on the nitrogen. The product of the oxidation of hordenine by a preparation from Scotch broom containing tyrosinase has been identified as *o*-hydroxyhordenine (3). The presence of tyrosinase in barley has been reported by several investigators (9, 19, 25), but James has recently proved that the enzyme does not occur in the rootlets, at least until the 11th day of germination (11). If, therefore, the conclusion that

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[2]*National Research Council of Canada Postdoctorate Fellow, 1954–1955.*

the tyrosinase occurs in some parts of the seedling other than in the rootlets is warranted, the presence of N-methyltyramine and hordenine in the rootlets can be explained. In the absence of tyrosinase, decarboxylation becomes the major pathway of tyrosine metabolism, and the product, tyramine, is methylated to form the alkaloids. This would account for the presence of hordenine solely in the roots, although tyrosine as shown by Raoul (19) is plentiful in the grain at the beginning of germination.

Certain microorganisms convert hordenine to *p*-hydroxyphenylethanol (5), while animal livers have been shown to transform hordenine, N-methyltyramine, and tyramine to *p*-hydroxyphenylacetic acid (7) and to *p*-hydroxyphenylethanol (18). These reactions have all been ascribed to oxidative deamination by the enzyme tyramine oxidase (21), but the presence of this enzyme in barley has not been demonstrated.

In the present work we have attempted to trace the path of hordenine metabolism in barley by feeding hordenine-α-C^{14} to the seedlings and following the radioactivity through an exhaustive fractionation.

EXPERIMENTAL

Hordenine-α-C¹⁴

Tyramine-α-C^{14} hydrochloride prepared as previously described (13) was dissolved in aqueous ammonia and the solution extracted with ether in a continuous extractor for 72 hr. The ether extract was evaporated and the residual oily base distilled, b.p. 120–130° at 0.01 mm. The base (137 mgm., 1.0 millimole), with a specific activity of 1.15×10^7 disintegrations per min. per millimole,[3] was methylated with formic acid and formaldehyde as described by Raoul (19). The hordenine-α-C^{14} thus obtained was sublimed at 120–130° at 0.01 mm., wt. 70.4 mgm. (44% yield). A paper chromatogram showed that tyramine and N-methyltyramine were absent from the product. It had a total activity of 4.77×10^6 d.p.m., and a specific activity of 1.12×10^7 d.p.m. per millimole.

Administration of Hordenine-α-C¹⁴ to Barley

Barley (Charlottetown No. 80, 720 gm. dusted with the fungicide Semesan) was grown as previously described (13) except that the seeds were spread on glass wool to minimize the growth of mold. The seeds were about two years old and had lost some of their germinative capacity (35–40% germination). On the sixth day of sprouting the barley was fed (as previously described (13), by addition to the germination trays) a solution of hordenine-α-C^{14} (70.4 mgm.) in water (600 ml.) containing concentrated hydrochloric acid (0.10 ml.). The administration of the alkaloid had no apparent ill effect on the growth of the barley. On the 11th day of sprouting the shoots were clipped off as near as possible to the root mat and dried at 70°, wt. 32 gm., and total activity less than 0.3×10^5 d.p.m. The glass wool mats containing the roots were dried at 110° without separation.

[3]*The activities were determined as thin samples with a Radiation Counters Laboratory "Nucleometer" making the usual corrections for self-absorption, etc.*

Extraction of Roots

The mats consisting of glass wool and the roots were cut into strips and extracted with methanol for 48 hr. The extract after evaporation of the methanol weighed 6.09 gm. and had a total activity of 1.01×10^6 d.p.m. (i.e., 21% of the activity of the hordenine fed to the barley). The roots were now extracted with three portions of 0.5 *N* sodium hydroxide by successive boiling for eight hours and filtering (1). After this treatment the roots were inactive. The three alkaline extracts had the following activities: 3.0×10^6, 6.3×10^5, and less than 0.3×10^5 d.p.m. respectively, totalling 76% of the activity administered. The sum of the activities of all the extracts amounted to 97% of the activity administered as labelled hordenine.

The methanol extract was suspended in water to which was added enough hydrochloric acid to make it acid to Congo red, and the mixture extracted with ether. The aqueous liquor was then treated as described previously (13) to isolate the hordenine (116.3 mgm., specific activity, 8.58×10^5 d.p.m. per millimole) and the N-methyltyramine (34.9 mgm., specific activity, 1.43×10^5 d.p.m. per millimole). Choline was separated from the liquor from which the alkaloids had been removed, via the reineckate by the usual method (12, 15), and isolated as the chloroplatinate. It was inactive. No candicine was present.

Fractionation of the Sodium Hydroxide Extract

The three sodium hydroxide extracts were filtered and acidified separately with 5 *N* sulphuric acid. Precipitates were formed in the first two only (Residue B). The two filtrates were combined with the clear extracts and the combined liquor concentrated to 3 liters, alkalized to litmus with sodium hydroxide, and neutralized with acetic acid. A gelatinous precipitate settled out which was removed by centrifugation (Residue C). The mother liquor was then freed of much of the salt it contained by alternate precipitation with ethanol and concentration. The precipitates were combined with Residue C. After this treatment the aqueous solution D measured 800 ml., was slightly acid to litmus, and had an activity of 8.28×10^5 d.p.m.

One quarter of this solution D was percolated through a cation exchanger (Dowex 50-X4, hydrogen form, chloride-free) and an anion exchanger (Amberlite IR-4B, hydroxyl form, neutral to litmus) contained in columns (40 cm. $\times$3.5 cm.) connected so that the effluate from the cation exchanger passed directly into the anion exchanger. Water was percolated through the assembly until 2 liters of percolate had been collected. The percolate included sugars and other neutral substances which were negligibly radioactive (less than 1.0×10^4 d.p.m.). The columns were disconnected and washed separately with 1 liter of water (washings inactive). The anion exchanger was then eluted with 3 liters of 0.2 *N* hydrochloric acid, giving 1.604 gm. of acids, also negligibly radioactive (less than 2×10^3 d.p.m.). Elution of the cation exchanger with 1 liter of 0.15 *N* ammonia gave a basic fraction (0.990 gm.) with an activity of 6.1×10^4 d.p.m. No further activity was detected on further elution with ammonia or with 0.1 *N* sodium hydroxide.

Fractionation of the Weak Bases

The radioactive eluate from the cation exchanger contained principally the weakly basic amino acids and gave a positive Millon test. It was chromatographed on a charcoal column (2 cm.×9 cm.) (22). The charcoal (Darco G-60, 5 gm.) was pretreated by being heated on the steam bath with 200 ml. of 20% acetic acid, was cooled and washed on a filter with water, and then was transferred to the column in a slurry with 5% acetic acid. The residue left after evaporation of the eluate from the cation exchanger was dissolved in 5% acetic acid (100 ml.) and the solution transferred to the column, which was later eluted with 5% acetic acid until 300 ml. of eluate had been collected. This eluate on evaporation *in vacuo* yielded the non-aromatic amino acids (1.545 gm., activity, 2500 d.p.m.). The charcoal column was further eluted with 300 ml. of a mixture of water, glacial acetic acid, and phenol in the proportion of 80:20:5 (22). This eluate was extracted with ether to remove the phenol and evaporated to dryness under diminished pressure, leaving a residue of aromatic substances (0.198 gm., activity, 5.9×10^4 d.p.m.). A paper chromatogram of the residue developed with 80% phenol and sprayed with ninhydrin showed that it contained phenylalanine and tyrosine, but no tryptophan.

Phenylalanine and Tyrosine

The aromatic fraction described above was dissolved in a small volume of 4 *N* hydrochloric acid, transferred to a column (1 cm.×50 cm.) of Dowex 50-X12 prepared according to Wall (28), and eluted with 4 *N* hydrochloric acid. The eluate was collected in 5 ml. fractions, and aliquots were chromatographed on paper to spot the amino acids, which were detected with ninhydrin. Fractions 20–48 and 54–84 contained tyrosine and phenylalanine respectively. Each of these two acids was dissolved in 5% acetic acid (5 ml.) and the solution percolated through columns of Dowex 1-X8 in the acetate form to convert the hydrochloride to the free bases (10). The two eluates (each 50 ml.) were evaporated to dryness. Neither the tyrosine (43.9 mgm.) nor the phenylalanine (53.4 mgm.) after recrystallization was radioactive.

Hordenine and N-Methyltyramine

The mother liquor from the first phenylalanine crystallization and fractions 85–154 from the Dowex 50–X12 column gave a strong Millon test. A paper chromatogram under conditions previously described (13) showed the presence of hordenine and N-methyltyramine, but no tyramine nor tyrosine. The combined fractions 85–154 (activity, 4.3×10^4 d.p.m.) were alkalized with ammonia and extracted with ether for 48 hr. The extract (activity, 3.3×10^4 d.p.m.) contained hordenine and N-methyltyramine. The alkaloids were isolated directly from the remaining three-quarters of solution D by alkalizing the solution with ammonia and extracting with ether in the usual manner. To this extract were added the bases obtained above and the solution chromatographed on alumina to separate the two alkaloids. After sublimation the hordenine weighed 22.8 mgm. and had the specific activity 6.28×10^5 d.p.m. per millimole, and the N-methyltyramine weighed 32.2 mgm. and had the specific activity 1.5×10^5 d.p.m. per millimole.

Lignin

Residue B (activity, 1.95×10^5 d.p.m.) was treated by the procedure of Bondi and Meyer (1) in order to isolate the lignin. The product, a brown amorphous powder weighing 0.704 gm., had a total activity of 0.96×10^5 d.p.m. or 136 d.p.m. per mgm. Found: ash, 1.47%; N (ash-free), 5.81%; OCH_3 (ash-free), 4.53%.

A sample of this lignin was oxidized with nitrobenzene and alkali as described by Stone and Blundell (26). A product was obtained which gave a brick-red derivative with 2,4-dinitrophenylhydrazine. This derivative was completely inactive, but could not be crystallized and was not further identified.

A further quantity of lignin was isolated from Residue C. This residue consisted of dark brown gelatinous material and salts. It was taken up in water (1 liter) and dialyzed for one week to remove the salts and any remaining substances of low molecular weight. The amorphous, insoluble material was collected by centrifugation, and stirred in 1.25 *N* sodium hydroxide (500 ml.). The alkali-soluble material was treated as before (1) and yielded 1.670 gm. of brown amorphous powder with an activity of 2.1×10^5 d.p.m. or 126 d.p.m. per mgm. No proof of the identity of the two lignin preparations was possible, but the activities per mgm. are in good agreement.

DISCUSSION

Since the methanol and the sodium hydroxide extracts together accounted for 97% of the activity fed to the plant as labelled hordenine, any loss to the air as carbon dioxide was negligible, and it appeared probable that hordenine was not degraded to one-carbon fragments, except for the methyl group. The only compounds isolated that were radioactive were hordenine, N-methyltyramine, and lignin. Hordenine was not broken down to fragments capable of taking part in sugar synthesis, for the sugars were inert. Phenylalanine and tyrosine were also inert, and no tyramine was present. Consequently hordenine seems to undergo a partial demethylation only, giving rise to N-methyltyramine. No recarboxylation of the bases back to amino acids takes place since the amino acids isolated were not radioactive.

It has been shown by Freudenberg and Bittner (8) and by Siegel (23) that simple C_6, C_3 compounds can be lignin precursors. More recently Siegel (24) has demonstrated that in the presence of cellulose, eugenol is converted by peroxidase – hydrogen peroxide to a polymeric substance giving positive color tests for lignin. Also, Brown and Neish (2) have shown that C_6, C_3 amino acids such as phenylalanine and tyrosine do act as lignin precursors.

It is known that the lignin of very young plants unlike that of older plants contains nitrogen which appears to be an integral part of it. The lignin of two-week-old barley seedlings has been stated to contain as much as 8% nitrogen by Phillips (17), who further showed that the nitrogen content fell steadily as the plants matured.

The isolation of radioactive lignin in the present investigation, where the

only source of C^{14} was the hordenine, indicates that a C_6, C_2 fragment can also take part in lignin synthesis. The results also lead to the inference that hordenine is the source of at least part of the nitrogen in barley lignin. This inference, however, can only be drawn with caution and will require more definite proof.

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THE SYSTEM LITHIUM CHLORATE – LITHIUM CHLORIDE – WATER AT VARIOUS TEMPERATURES[1]

By A. N. Campbell and J. E. Griffiths[2]

ABSTRACT

The equilibrium diagram of the system lithium chlorate – water has been determined at all temperatures and that of the system lithium chlorate – lithium chloride – water at the temperatures 3.0°, 6.0°, 8.5°, and 25.0° C.

Lithium chlorate forms three hydrates having the formulae:

(i) $(LiClO_3)_4.H_2O$—stable in contact with solution from 20.5° to 42.0° C.

(ii) $LiClO_3.H_2O$—stable in contact with solution from −0.1° to 20.5° C.

(iii) $LiClO_3.3\ H_2O$—melts congruently at 8.4° C.

Hydrate (i) was discovered by Berg but he gave to it the formula $(LiClO_3)_3.H_2O$.

Lithium chlorate and lithium chloride form no double salts at the temperatures of investigation.

Lithium chlorate exists in two enantiotropic forms, namely the α and the β forms. The transition, $\alpha \leftrightarrow \beta$, takes place at 99.8° C. and the α form has the lower density. The γ form, proposed by Kraus and Burgess, does not exist either stably or metastably. The X-ray diffraction pattern of β-$LiClO_3$ has been obtained.

The question of the number and nature of the hydrates of lithium chlorate, after passing through the usual period of ill-founded claims, was attacked in a systematic manner by Kraus and Burgess (5) and by Berg (1), in the period 1926 to 1929. Almost all of the experimental data of these researches are in good agreement but the authors differ, in some respects, regarding their interpretation. Kraus and Burgess claim the existence of three anhydrous modifications, of a trihydrate, and of a monohydrate. Berg claims only two anhydrous modifications and three hydrates, viz. a hydrate with $\frac{1}{3}$ mole water per mole of salt, a monohydrate, and a trihydrate. In short, the two investigators differ in that Kraus and Burgess claim the existence of a γ-anhydrous form, between 22° and 44° C., where Berg claims a hydrate with $\frac{1}{3}$ mole water; in other respects they agree.

In order to decide the conflicting interpretation given above, as well as to verify the formulae of all hydrates, we decided to add a third ion to the binary system $LiClO_3$–H_2O, and to investigate the system $LiClO_3$–$LiCl$–H_2O, at various temperatures. Under these circumstances, the Schreinemakers' "wet rest" method determines the composition of all hydrates without ambiguity. In addition, we thought it well to repeat part of the work of Kraus and Burgess and of Berg, on the binary system. We have also made attempts, more or less successful, to obtain X-ray diffraction patterns of the phases in dispute. Finally, we attempted to determine transition temperatures with the dilatometer since this is the most delicate method of determining transition temperatures, but here again we were not entirely successful because of obstinate metastability.

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Contribution from the Chemistry Department, University of Manitoba, Winnipeg, Manitoba.
[2]*N.R.C. Bursar, 1955–56.*

EXPERIMENTAL

Lithium chlorate was prepared by a method which is essentially that of Potilitzin (6) and of Kraus (5), viz. double decomposition between barium chlorate and lithium sulphate, but the final dehydration to anhydrous salt is a modification of our own. The suppliers' analyses, both of lithium sulphate and of barium chlorate, showed that these salts were very pure; as the method of preparation of the anhydrous salt does not permit recrystallization this is a necessity, as is also the use of exact stoichiometric quantities.

A 1 molar solution of barium chlorate was heated to about 85° C., and a 1 molar lithium sulphate solution was added slowly to this with a dropping funnel until equivalence was reached. The precipitated barium sulphate was removed by repeated filtration. To ensure equivalence of lithium and chlorate ions, the resulting solution was titrated with dilute solutions of barium chlorate and lithium sulphate.

The solution was evaporated slowly, the temperature being kept below 85° C., up to an approximate concentration of 50% lithium chlorate. The filtered solution was transferred to a 250 ml. Claissen flask and dehydration was carried out under a reduced pressure of less than 5 mm. mercury, the distillate being absorbed in concentrated sulphuric acid. The temperature was kept below 85° C., since decomposition begins at this temperature in concentrated solutions. The result of this procedure was a solution containing about 90% lithium chlorate.

On the cooling of the solution to room temperature, the salt crystallized; it was placed under vacuum over phosphorus pentoxide. After about a month, the water content had been reduced to about one per cent. To remove the last trace of water, the salt was placed in a vacuum furnace, over phosphorus pentoxide, and kept at a temperature of 80° C. After several months, no further change was found in the melting point of the salt.

None of the textbook methods for the analysis of lithium chlorate is entirely satisfactory, so we worked out the following method: A weighed sample of lithium chlorate is made up to a volume of 250 ml. A 10, 20, or 25 ml. aliquot is transferred to a 250 ml. iodine flask. To this is added 40 ml. concentrated orthophosphoric acid, followed by the addition of about 0.1 gm. sodium carbonate, to exclude air from the flask. Approximately 25 ml. of iodate-free potassium iodide solution (0.2 gm./ml.) is added and the stoppered flask allowed to stand at room temperature for 60 to 70 min. The free iodine is titrated with sodium thiosulphate. Standardization of the method with pure sodium chlorate indicated an accuracy of $\pm 0.4\%$.

The chloride content of solutions containing appreciable amounts of chloride was determined volumetrically with silver nitrate solution, using an alcoholic solution of sodium dichlorofluoresceinate as indicator (4). For solutions containing less than five per cent chloride the standard gravimetric method was used.

Solubility determinations were made in the usual way. For temperatures below room temperature a cooled and controlled thermostat was used. Temperature control was good to ± 0.05° C. throughout this research

Thermal analysis was used only for the ice curve, the binary eutectics, and $\alpha \leftrightarrow \beta$ transition. After a break had occurred on the cooling curve, a sample of the equilibrium mother liquor was removed for analysis. Temperature was measured with an iron–constantan thermocouple and a good potentiometer.

The technique of X-ray diffraction measurements is now standard but, in the case of anhydrous lithium chlorate, measurements were rendered difficult by the very hygroscopic nature of the substance (it is comparable with that of phosphorus pentoxide). A sample of the anhydrous salt was ground to a fine powder and then returned to the vacuum desiccator and redried for several days. Following this, a very fine and thin-walled capillary tube (outside diameter 0.5 mm. and inside diameter 0.3 mm.) was filled with the sample and immediately sealed at both ends. The intensities of the lines were estimated visually. Powder photographs were taken of a sample that had been in a vacuum desiccator at room temperature for seven months and which we therefore considered to be the form stable at room temperature. A quantity of the same substance was then placed in another vacuum desiccator, held at 80° C. for a week, and then photographed: the results obtained were the same as for the unheated sample.

By means of a high temperature X-ray camera, we were able to take X-ray patterns at 115±5° C. We supposed that, at this temperature, the anhydrous lithium chlorate would have transformed to a different allotrope which would exhibit a different pattern. The result was disappointing; as far as could be judged, the pattern was the same as that at room temperature but the weaker lines of the room temperature picture had vanished and the few lines which did appear were quite broad. This is what would be expected if the lattice structure were the same. The atoms of the lattice would have increased thermal vibration at the higher temperature. A sample of the anhydrous lithium chlorate was sent to the National Research Council at Ottawa for further X-ray study. The work was carried out by Dr. L. D. Calvert, who was able to obtain diffraction patterns of the β form up to the melting point of the salt. Dr. Calvert was unable to detect any change in lattice structure corresponding to the change from the β to the α form, but his apparatus was not susceptible of close temperature control. At higher temperatures, however, he was able to evacuate his camera and this reduces the absorption of X rays by the air. The capillaries used in his work had a wall thickness of 0.007 mm.

The dilatometric work was carried out much in the usual manner. The bulb of the dilatometer had a stoppered side-tube to facilitate filling. The dilatometer was filled in a dry-box. About 100 gm. of anhydrous lithium chlorate, which had been dried for five months, was used to fill the bulb to about three-fourths capacity. The indicator liquid was *p*-xylene which had been dried over sodium for three days. The bulb of the dilatometer was placed in a thermostat whose temperature was constant to ±0.1° C. The temperature was raised one degree every 24 hr., but in the range 35° to 50° C., where Kraus and Burgess have claimed an allotropic transformation (5), the rate of increase was reduced to 0.5° per 24 hr. No break occurred on the curve of capillary height versus temperature, up to 106° C., with rising temperature. Since it was still

possible that a very slow transition had been overlooked, the temperature was kept at 60° C. for a week but there was still no indication of an $\gamma \rightarrow \beta$ transition. At higher temperatures an $\alpha \rightarrow \beta$ transition occurred and this was reversible. The formation of the α modification from the β modification is accompanied by a marked expansion but the change, in both directions, showed marked hysteresis.

THE SYSTEM LITHIUM CHLORATE – WATER

Since the part of the diagram where ice and solution were in equilibrium was of little interest, this was outlined by the method of thermal analysis. The compositions of the solutions in equilibrium with ice at various temperatures were determined by chemical analysis. With the exception of a few fixed points the rest of the equilibrium diagram was investigated by isothermal solubility determinations. The solubilities covered the range of composition

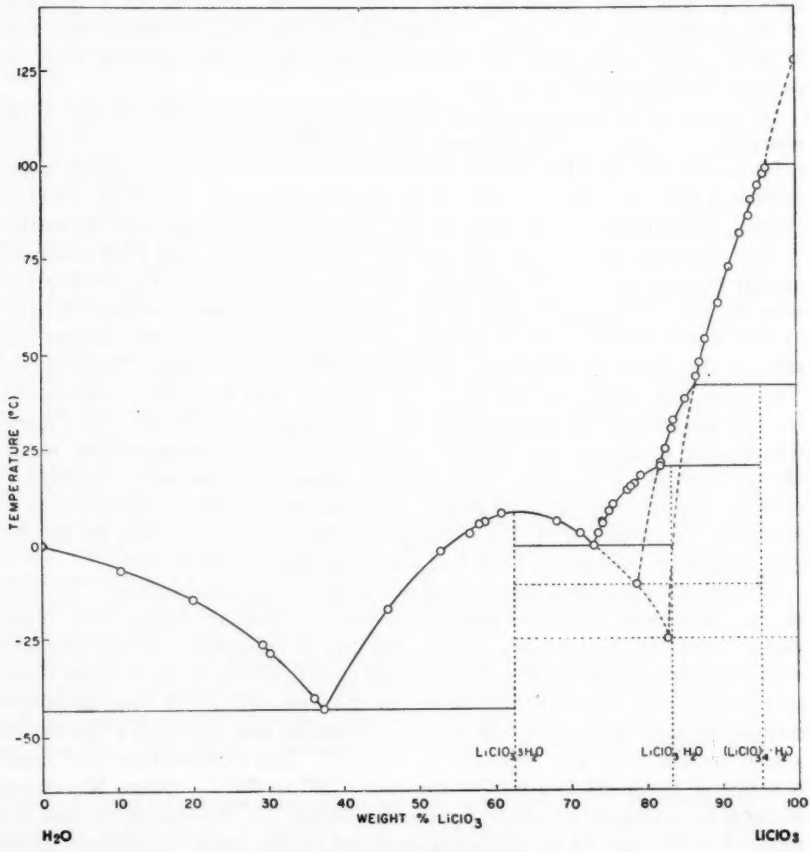


FIG. 1. System $LiClO_3$–H_2O.

from 45.8 to 95.5 weight per cent lithium chlorate. The upper temperature reached was 98.9° C. The determinations were discontinued at this point because the change of solubility per degree rise in temperature had become less than the accuracy of the analysis.

The stable and metastable binary eutectics were determined by thermal analysis in the usual way. The thermal analysis of the anhydrous salt was conducted in an evacuated vessel, with a copper–constantan thermocouple and a Minneapolis–Honeywell recording potentiometer. The temperature was raised slowly to a temperature above the melting point and the melt then allowed to cool slowly. The experiment was repeated many times in the vicinity of 40° C., because of the $\beta \leftrightarrow \gamma$ transition which is said to occur there.

EXPERIMENTAL RESULTS

The solubility relations and the results of thermal analyses are reported in Table I, together with the method used to arrive at them. The equilibrium diagram is shown in Fig. 1. The broken lines indicate solubility curves in the metastable region. A broken vertical line represents the composition of a hydrate. Since the solubility of lithium chlorate in water was not determined at temperatures above 98.9° C., the part of the solubility curve representing α-lithium chlorate in equilibrium with solution from 98.9° C. to 127.5° has been drawn in as a broken line.

TABLE I

THE SYSTEM $LiClO_3$–H_2O

	Wt. % $LiClO_3$	Wt. % H_2O	Method	Temperature (° C.)	Nature of the solid phases
1	—	100.0	Thermal analysis	0.0	Ice
2	10.4	89.6	"	− 6.5	"
3	20.0	80.0	"	−14.2	"
4	29.2	70.8	"	−26.2	"
5	30.2	69.8	"	−28.6	"
6	36.0	64.0	"	−40.4	"
7	37.3	62.7	"	−43.3	Ice–$LiClO_3.3H_2O$ (eutectic)
8	45.8	54.2	Solubility	−16.9	$LiClO_3.3H_2O$
9	52.8	47.2	"	− 1.5	"
10	56.7	43.3	"	3.0	"
11	57.9	42.1	"	5.2	"
12	58.7	41.3	"	6.0	"
13	60.8	39.2	"	8.1	"
14	68.1	31.9	"	6.0	"
15	70.8	29.2	"	3.0	"
16	73.1	26.9	Thermal analysis	− 0.1	$LiClO_3.3H_2O$–$LiClO_3.H_2O$ (eutectic)
17	73.6	26.4	Solubility	3.0	$LiClO_3.H_2O$
18	74.2	25.8	"	5.6	"
19	74.1	25.9	"	6.0	"
20	75.1	24.9	"	8.5	"
21	75.7	24.3	"	10.5	"
22	77.5	22.5	"	14.0	"
23	78.0	22.0	"	15.0	"
24	78.5	21.5	"	16.0	"
25	79.3	20.7	"	18.0	"
26	81.9	18.1	"	20.5	$LiClO_3.H_2O$–$(LiClO_3)_4.H_2O$ (peritectic)

TABLE I (*concluded*)

	Wt. % $LiClO_3$	Wt. % H_2O	Method	Temperature (° C.)	Nature of the solid phases
27	82.0	18.0	Solubility	21.5	$(LiClO_3)_4.H_2O$
28	82.6	17.4	"	25.0	"
29	83.4	16.6	"	30.2	"
30	83.6	16.4	"	32.6	"
31	85.2	14.8	"	38.5	"
32	78.7	21.3	Thermal analysis	−10.5	$LiClO_3.3H_2O$–$(LiClO_3)_4.H_2O$ (eutectic)
33	82.7	17.3	"	−25.0	$LiClO_3.3H_2O$–β-$LiClO_3$ (eutectic)
34	86.7	13.3	Solubility	44.2	β-$LiClO_3$
35	87.2	12.8	"	47.9	"
36	87.8	12.2	"	54.0	"
37	89.5	10.5	"	63.2	"
38	91.0	9.0	"	72.8	"
39	92.4	7.6	"	81.7	"
40	93.7	6.3	"	86.2	"
41	93.8	6.2	"	90.7	"
42	94.8	5.2	"	94.2	"
43	95.5	4.5	"	97.5	"
44	95.9	4.1	"	98.9	"
45	100.0	0.0	Thermal analysis	127.5	α-$LiClO_3$

Since Calvert's results for the X-ray diffraction pattern of lithium chlorate at room temperature are in agreement with ours but his are more extensive, we reproduce only Calvert's results, in Table II.

In regard to the dilatometer results, it is sufficient to say that the $\beta \rightarrow \alpha$ transformation took place at 108° and at 106° in two successive cycles with rising temperature, and that the reverse change, $\alpha \rightarrow \beta$, took place at 80° C. and 84.1° C.

The results of the thermal analysis of the anhydrous salt are contained in Table III.

The System Lithium Chlorate – Lithium Chloride – Water

It was found that the time of stirring required for the attainment of equilibrium varies considerably, depending on the nature of the equilibrium solid phase or phases. Because of this uncertainty, equilibrium was always approached from two directions. A mixture of appropriate composition was divided into equal parts and treated as follows. One part was heated until all the solid phase had passed into solution, whereas the other was frozen until all the solution had solidified. These two portions were then stirred in tubes in the thermostat until the compositions of the liquid phases in each portion had become identical. For solutions containing up to 10% lithium chloride, the equilibrium stirring time was found to be from two to three days. When the solutions were more concentrated in lithium chloride, and particularly when the solid phase was the monohydrate or dihydrate of lithium chloride, five or six days were necessary for the attainment of equilibrium.

Solubility isotherms were determined at 3.0°, 6.0°, 8.5°, and 25.0° C., employing the Schreinemakers' method of "wet residues" for the determination of the nature of the equilibrium solid phase.

TABLE II

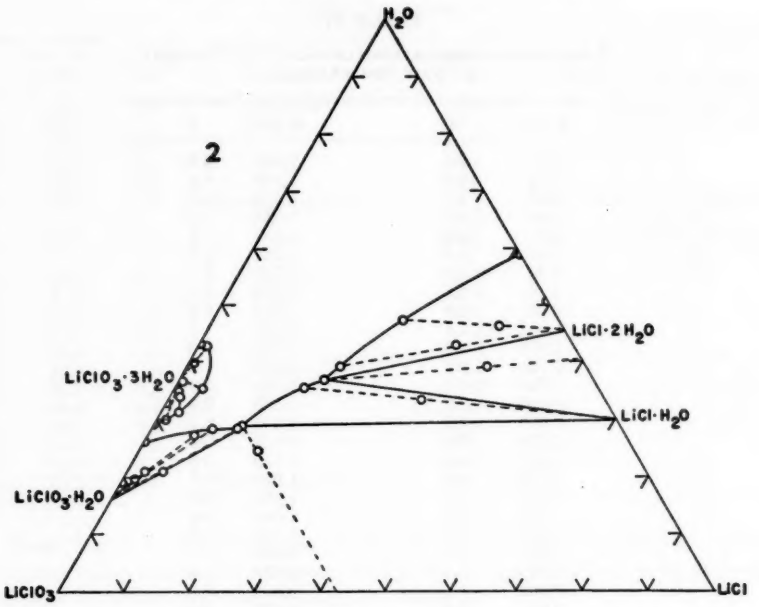
X-RAY DIFFRACTION PATTERN OF β-$LiClO_3$ (CALVERT) AT ROOM TEMPERATURE

d (kX)	I	d (kX)	I
3.91	9.5	1.441	4.0
3.79	10.0	1.428	0.4
3.42	9.0	1.416	0.5
2.81	10.0	1.378	1.0
2.71	8.0	1.337	1.4
2.39	3.0	1.331	1.7
2.26	3.4	1.322	0.7
2.13	2.7	1.295	3.0
2.05	0.9	1.255	0.9
1.947	1.1	1.236	1.1
1.879	1.3	1.223	1.0
1.795	0.9	1.213	1.0
1.726	1.1	1.188	1.0
1.665	3.2	1.153	0.9
1.629	1.3	1.140	0.4
1.576	0.9	1.128	0.6
1.549	1.1	1.119	0.8
1.539	1.0	1.078	0.7
1.510	1.1	1.064	0.6
1.500	2.0	1.060	0.9
1.469	0.9	1.040	0.9
1.027	3.5	0.836	1.1
1.025	2.6	0.834	1.0
0.993	1.1	0.831	2.5
0.991	0.9	0.829	2.0
0.985	0.5	0.824	2.1
0.975	0.5	0.822	1.1
0.972	0.5	0.818	1.4
0.969	0.5	0.816	0.4
0.967	0.5	0.812	0.4
0.954	1.6	0.807	0.2
0.933	1.2	0.805	1.7
0.931	1.0	0.803	1.5
0.926	0.2	0.801	1.4
0.923	0.3	0.794	1.6
0.920	0.2	0.792	1.4
0.901	0.8	0.788	1.4
0.898	0.7	0.787	0.6
0.888	0.6	0.784	0.6
0.847	1.0	0.782	2.0
0.844	0.9	0.780	0.5
0.841	0.8	0.774	2.6
0.839	0.6		

TABLE III

THERMAL ANALYSIS OF ANHYDROUS SALT

Rising temperature		Falling temperature	
Transformation	Temperature (° C.)	Transformation	Temperature (° C.)
$\alpha \rightarrow$ Melt	127.4–127.5	Melt $\rightarrow \alpha$	127.4–127.5
$\beta \rightarrow \alpha$	106.1	$\alpha \rightarrow \beta$	98.2
$\beta \rightarrow \alpha$	103.6	$\alpha \rightarrow \beta$	99.8



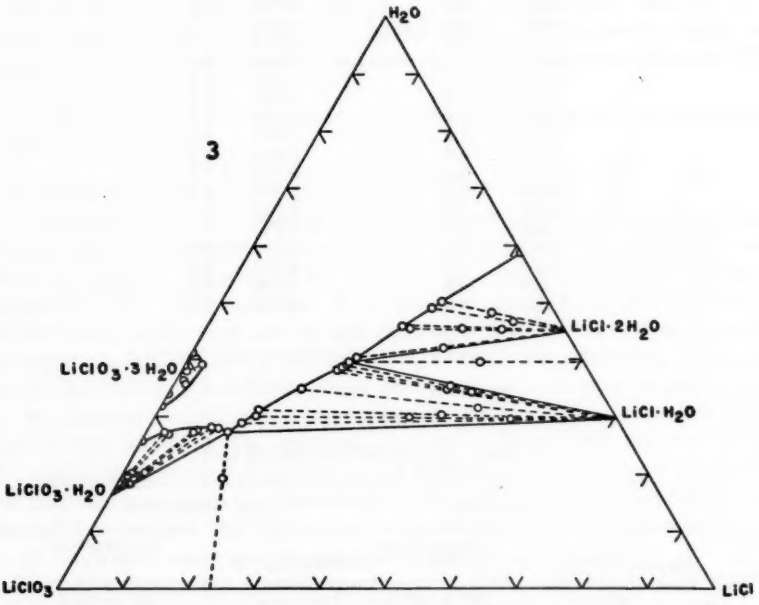
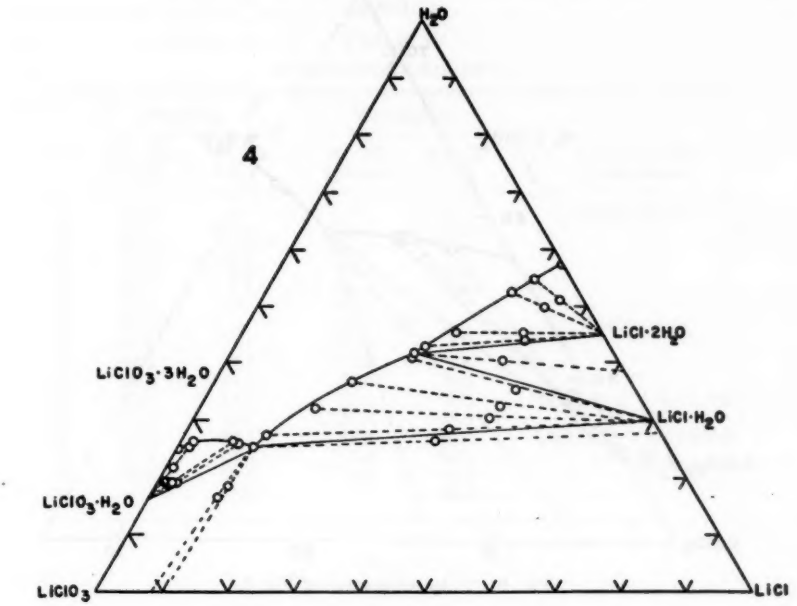


FIG. 2. System $LiClO_3$–LiCl–H_2O at 3.0° C.
FIG. 3. System $LiClO_3$–LiCl–H_2O at 6.0° C.



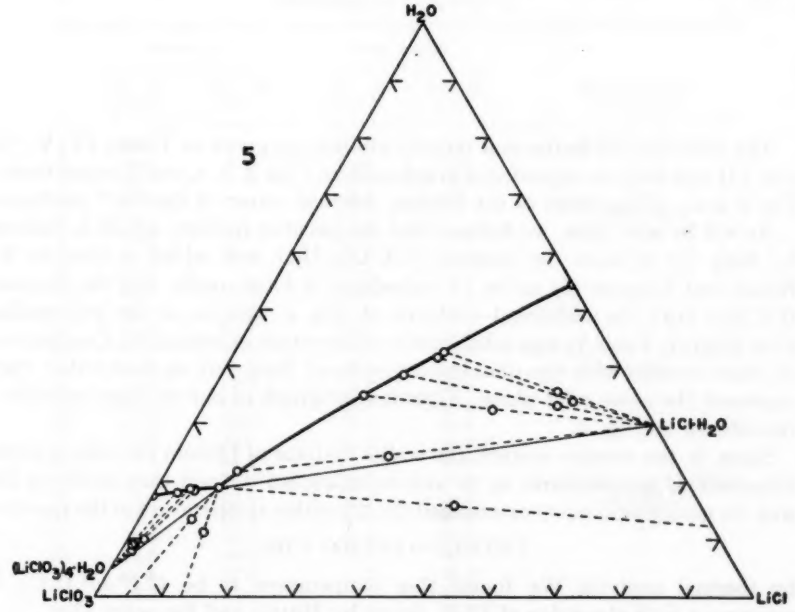


FIG. 4. System $LiClO_3$–LiCl–H_2O at 8.5° C.
FIG. 5. System $LiClO_3$–LiCl–H_2O at 25.0° C.

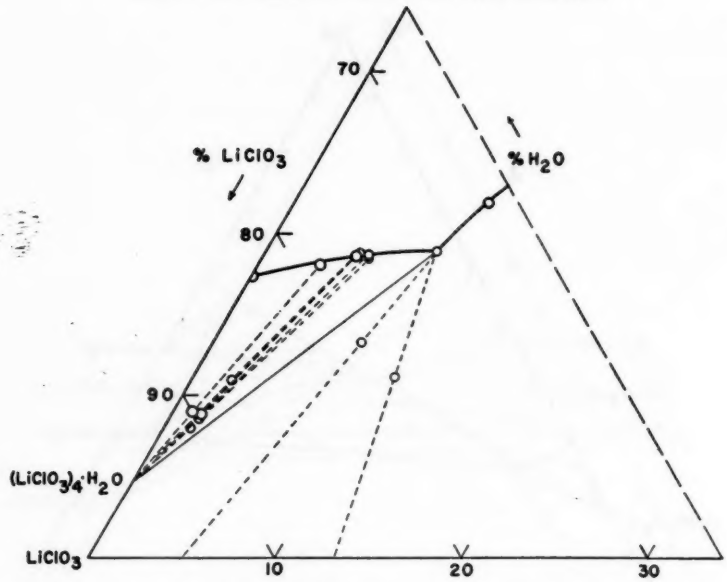


FIG. 6. Enlarged portion of Fig. 5.

The data for the isothermal ternary studies are given in Tables IV, V, VI, and VII and they are reproduced graphically in Figs. 2, 3, 4, and 5, respectively. Fig. 6 is an enlargement of the lithium chlorate corner of the 25.0° isotherm.

As will be seen later, we believe that the peculiar hydrate which is claimed by Berg (1) to have the formula $(LiClO_3)_3.H_2O$, and which is thought by Kraus and Burgess (5) to be an anhydrous γ form, really has the formula $(LiClO_3)_4.H_2O$. As additional evidence of this, a sample of the wet residue from Expt. 7, Table V, was submitted to microscopic examination. Comparison of these crystals with the photomicrographs of Berg, left no doubt that they represent the same solid phase. A photomicrograph of one of these crystals is reproduced as Fig. 7.

Since, in the ternary system, the stable hydrate of lithium chloride was the dihydrate at temperatures up to and including 8.5° C. and that stable at 25° was the monohydrate, we determined the transition temperature of the reaction

$$LiCl.2H_2O \leftrightarrow LiCl.H_2O + H_2O$$

by thermal analysis. We found this temperature to be 12.5°±0.1° C., in agreement with the value of 12.5°, found by Hüttig and Reuscher (3).

RESULTS

TABLE IV

ISOTHERM FOR 3.0±0.05° C.

	Solution		Wet residue		
	Wt. % $LiClO_3$	Wt. % LiCl	Wt. % $LiClO_3$	Wt. % LiCl	Nature of the solid phase
1	56.7	—	—	—	$LiClO_3.3H_2O$
2	55.8	1.3	59.4	0.9	"
3	62.2	4.3	62.7	0.7	"
4	66.0	2.8	64.5	1.6	"
5	68.7	1.5	64.1	0.8	"
6	70.8	—	67.0	—	"
7	73.6	—	80.7	—	$LiClO_3.H_2O$
8	65.6	7.1	78.4	1.9	"
9	62.4	9.4	76.2	3.8	"
10	58.5	13.1	73.6	5.6	"
11	57.5	13.7	57.1	18.1	$LiClO_3.H_2O$ + $LiCl.H_2O$
12	44.7	19.9	27.9	38.8	$LiCl.H_2O$
13	40.9	22.1	15.0	46.0	$LiCl.H_2O$ + $LiCl.2H_2O$
14	37.4	23.5	17.8	39.3	$LiCl.2H_2O$
15	23.9	29.1	9.6	44.2	"
16	—	41.0	—	49.3	"

TABLE V

ISOTHERM FOR 6.0±0.05° C.

	Solution		Wet residue		
	Wt. % $LiClO_3$	Wt. % LiCl	Wt. % $LiClO_3$	Wt. % LiCl	Nature of the solid phases
1	58.7	—	61.1	—	$LiClO_3.3H_2O$
2	58.3	2.5	61.3	0.8	"
3	62.7	1.8	62.7	1.0	"
4	68.1	—	66.1	—	"
5	74.1	—	81.4	—	$LiClO_3.H_2O$
6	70.0	2.7	79.5	0.9	"
7	69.7	3.4	78.6	1.2	"
8	65.8	7.1	79.9	1.9	"
9	64.9	7.5	78.8	2.0	"
10	62.6	9.6	76.5	3.1	"
11	61.4	10.7	78.0	2.2	"
12	60.4	12.3	65.1	15.6	$LiClO_3.H_2O$ + $LiCl.H_2O$
13	57.5	13.7	16.0	54.3	$LiCl.H_2O$
14	54.8	15.2	31.4	38.9	"
15	53.9	15.0	26.2	43.5	"
16	45.2	20.0	20.0	48.2	"
17	38.2	23.7	23.2	42.0	"
18	37.2	24.0	19.7	46.0	"
19	36.2	24.6	22.2	42.3	$LiCl.H_2O$ + $LiCl.2H_2O$
20	35.7	24.9	16.6	44.8	$LiCl.2H_2O$
21	34.1	25.4	20.0	37.8	"
22	24.4	29.7	15.5	39.0	"
23	23.5	30.0	9.7	45.1	"
24	18.3	32.5	7.1	46.0	"
25	16.3	33.5	7.1	42.0	"
26	—	41.1	—	49.5	"

TABLE VI

ISOTHERM FOR 8.5±0.05° C.

	Solution		Wet residue		
	Wt. % $LiClO_3$	Wt. % LiCl	Wt. % $LiClO_3$	Wt. % LiCl	Nature of the solid phases
1	75.0	—	—	—	$LiClO_3.H_2O$
2	73.4	1.5	77.5	0.9	"
3	72.0	1.9	80.0	0.8	"
4	66.1	7.7	79.0	2.0	"
5	65.6	8.8	78.3	2.5	"
6	64.2	11.2	70.7	11.9	$LiClO_3.H_2O + LiCl.H_2O$
7	63.5	11.2	73.3	11.2	"
8	62.7	11.6	35.1	38.4	"
9	60.5	12.3	31.9	39.7	$LiCl.H_2O$
10	50.8	17.4	24.9	44.9	"
11	31.3	27.7	18.3	46.3	"
12	30.6	27.8	17.8	41.9	$LiCl.H_2O + LiCl.2H_2O$
13	28.2	28.9	12.8	43.4	$LiCl.2H_2O$
14	22.5	32.2	12.2	42.7	"
15	10.4	37.3	6.7	43.7	"
16	5.6	39.7	3.8	45.3	"
17	—	42.7	—	50.3	"

TABLE VII

ISOTHERM FOR 25.0±0.05° C.

	Solution		Wet residue		
	Wt. % $LiClO_3$	Wt. % LiCl	Wt. % $LiClO_3$	Wt. % LiCl	Nature of the solid phases
1	82.6	—	—	—	$(LiClO_3)_4.H_2O$
2	78.7	3.3	90.0	1.0	"
3	76.4	5.0	89.6	1.6	"
4	76.1	5.1	86.9	2.1	"
5	75.7	5.6	89.9	1.5	"
6	75.8	5.7	87.8	2.3	"
7	75.9	5.8	90.7	1.4	"
8	72.3	9.2	78.8	8.0	$(LiClO_3)_4.H_2O + LiCl.H_2O$
9	71.8	9.2	78.1	10.8	"
10	71.6	9.2	37.5	46.7	"
11	67.7	10.7	43.1	32.4	$LiCl.H_2O$
12	41.7	23.3	23.2	44.4	"
13	33.8	27.7	13.0	53.8	"
14	27.0	31.3	10.1	55.7	"
15	25.5	31.7	11.7	52.5	"
16	—	45.5	—	—	"

DISCUSSION OF RESULTS

Apart from a few slight refinements in temperature and composition, the solubility curves in the binary equilibrium diagram, Fig. 1, are essentially the same as those previously obtained by Kraus and Burgess (5) and by Berg (1). In general, the results of previous workers indicate a lower solubility than do our results.

The trihydrate of lithium chlorate melts congruently but the equilibrium curve is very flat and this makes it difficult to read off the exact melting

temperature from the curve. Neither was an attempt to determine the melting point by direct experiment successful, since it is difficult to prepare and maintain the mixture having the exact composition of the trihydrate. We found, experimentally, that the trihydrate exists at 8.1°, while reference to Fig. 4, the 8.5° isotherm, shows that trihydrate is absent. The flat maximum on the equilibrium curve, as well as we could read it, appeared to us to lie at 8.4° C. Kraus and Burgess (5) reported 8.0° and Berg (1) from 8.1 to 8.3°.

The trihydrate participates in four eutectics, two stable ones at −43.3° and −0.1° C. respectively, and two metastable at −10.5° and −25° respectively. The other solid phases at the eutectics are listed in Table I.

The solubility curves of the binary system indicate that two different solid phases are in equilibrium with solution in the temperature ranges −0.1° to 20.5° C. and 20.5° to 42.0°, respectively. The ternary isotherms for 3.0°, 6.0°, 8.5°, and 25.0° show clearly what the phases are. In the lower temperature range, the solid phase is the monohydrate of lithium chlorate, as claimed by Kraus and Burgess and by Berg.

The isothermal ternary study at 25.0° proved to be the most instructive, since it has refuted the claims both of Kraus and Burgess and of Berg. Fig. 6, which is an enlargement of the lithium chlorate corner of the 25° isotherm, shows tie lines running consistently into a composition corresponding to the hydrate $(LiClO_3)_4.H_2O$. Since the existence or non-existence of this hydrate is important, it is well to say a few words about the attainable experimental accuracy in this region. The successful application of the Schreinemakers' method of "wet residues" depends on the accuracy of the chemical analyses employed and on the extent to which mother liquor is removed from the "wet" solid phase. At 25°, we never found more than 11% water in this solid phase; this could hardly be improved upon, since the dry hydrate itself contains 4.7% water. Although the inaccuracy of our chlorate determinations may amount to 0.4%, our gravimetric determinations of chloride were much better than this. In Fig. 6, the tie lines joining the compositions of the liquid phase and the wet residue cross the lithium chlorate reference lines at an angle of about 70°. Hence, if there is an error of 0.4% in the lithium chlorate determination this would lead to an error of about 0.2% lithium chlorate in the composition of the equilibrium solid phase. The consequences of an error in the lithium chloride analysis are far more serious, because the directions of the tie lines and the reference line of lithium chloride approach one another. The fact that none of the tie lines ever crossed, and that they all converged to a single composition when extrapolated, indicates that the analyses were of sufficient accuracy and that equilibrium had been reached in all cases. As a check on the possibility of any consistent error in the procedure, the data were compared with a point which had been determined a month previously. The points all indicated the same solid phase and therefore left no doubt that the hydrate stable at 25° C. has the composition corresponding to the formula $(LiClO_3)_4.H_2O$.

In Fig. 6 there are no experimentally determined solubilities representing solutions containing from 5.8 to 9.16% lithium chloride. In order to prove that

a break did not occur in the solubility curve in this range, the wet residues from the two determinations 7 and 8 were investigated under the polarizing microscope. The solid phase was the same in both cases, although a slight amount of the monohydrate of lithium chloride was present in number 8. Therefore, the invariant solutions 8, 9, and 10 were actually in equilibrium with the one-fourth hydrate of lithium chlorate and the monohydrate of lithium chloride.

The hydrate which Berg claims contains one-third of a mole of water we think contains only one-fourth of a mole of water, but we are referring to the same hydrate. We convinced ourselves of this by comparing our photomicrograph of wet residue 7 with those obtained by Berg of his supposed one-third hydrate. If, therefore, our hydrate contains one-fourth of a mole of water, so does Berg's. Berg deduced the composition of his hydrate by the method of the peritectic halt time and this is far from being a sensitive method. Kraus and Burgess, on the other hand, thought they had eliminated Berg's claim for a hydrate of low water content on the ground that a mixture containing 6.55% water definitely showed the presence of solution between 21.0° and 41.5° C. If the solid were really the one-third hydrate, which contains 6.2% water, the mixture would not form an observable amount of solution. If, however, the hydrate contains only one-fourth of a mole of water, as we claim, about one-third of the above mixture would liquefy.

At 42.0° C., the one-fourth hydrate undergoes a peritectic transition to anhydrous salt and solution. The modification of anhydrous salt formed at 42° C. is the first (low temperature) modification of two allotropic forms. This form is the one stable at room temperature and corresponds to the β form of Kraus and Burgess. Of the three methods used to investigate the transition from β to α, viz. thermal analysis, dilatometry, and X-ray diffraction, only the former method gave a really satisfactory result and it indicated that the transition temperature was 99.8° C. This value compares favorably with the values obtained by Kraus and Burgess and by Berg. The dilatometer showed a marked increase in volume, accompanying the β to α transition. We have applied the techniques of dilatometry, thermal analysis, solubility, and X-ray diffraction in an attempt to find the supposed β to γ transition, but always without result. The heating and cooling curves of anhydrous salt showed no break and the expansion and contraction of the dilatometer was perfectly regular. Finally, an X-ray diffraction picture was taken of a sample which had never been heated; this was then heated for a week at 80° C., allowed to cool, and immediately photographed again. The two patterns were identical.

If the hemihydrate of lithium chlorate claimed by Wächter (8), Troost (7), Potilitzin (6), and Brühl (2) did indeed exist, it would be formed from the monohydrate in a peritectic transformation. This would appear as a break in the solubility curve, in the binary system. No such break occurred between −0.1° and 20.5° C. The monohydrate is the solid phase in equilibrium with solution in this temperature interval. Neither was there any break in the solubility curve from 20.5° to 42° C. In this temperature range, the stable solid phase is the one-fourth hydrate. Therefore, there is no doubt that the

hemihydrate of lithium chlorate does not exist as a stable phase and there have been no indications of its ever appearing as a metastable phase throughout this study.

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A STUDY OF THE REACTIONS OF AMMONIUM SULPHAMATE WITH AMIDES AND UREAS[1]

By Paul E. Gagnon, Jean L. Boivin,[2] and Catherine Haggart[3]

ABSTRACT

The preparation of nitriles from amides and ammonium sulphamate was investigated. The method was found to be generally applicable and good yields were obtained in most cases. The mechanism of the reaction involved the liberation of ammonia and the formation of ammonium N-carbonyl sulphamates, which decomposed into nitriles and ammonium bisulphate.

The mechanism for the formation of guanidine and cyanuric acid from ureas was elucidated. The effects of methyl, phenyl, acetyl, and benzoyl groups on the reactivity of the urea molecule were determined. Methylamine and aniline were obtained from methylurea and phenylurea together with guanidine and cyanuric acid. Acetylurea and benzoylurea formed acetonitrile and benzonitrile, the yield of guanidine being low but that of cyanuric acid very high.

INTRODUCTION

Amides and Ammonium Sulphamate

Nitriles had been obtained before from amides by treatment with phosphorus pentachloride, phosphorus pentoxide, phosphorus oxychloride, and thionyl chloride. Short and long chain aliphatic and aromatic amides required the use of different dehydrating agents.

In 1950 Boivin (2) reported that nitriles were formed when simple aliphatic and aromatic amides (I) were heated with ammonium sulphamate (II) at 180–190° C. The reaction proceeded with the evolution of ammonia and the formation of ammonium bisulphate.

$$\underset{\text{I}}{RCONH_2} + \underset{\text{II}}{H_2NSO_3NH_4} \rightarrow RCN + NH_4HSO_4 + NH_3$$

In order to determine whether this method of preparing nitriles was generally applicable, a series of amides, including short and long chain aliphatic, aromatic, α-substituted aliphatic, and heterocyclic amides were heated with ammonium sulphamate. The corresponding nitriles were obtained in fairly good yields. They are listed in Table I.

It was known that ammonium sulphamate did not behave as a normal dehydrating agent (3). Berglund (1) found that when heated alone at 170–180° C. it was transformed into ammonium imidodisulphonate (III) and ammonia.

$$2\ H_2NSO_3NH_4 \rightarrow \underset{\text{III}}{HN(SO_3NH_4)_2} + NH_3$$

This showed that there was the possibility of the formation of an intermediate when amides were heated with ammonium sulphamate. The possibility was

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substantiated during the present work. In fact, it was found that mixtures of amides and ammonium sulphamate when heated directly at 200° C. produced nitriles in very low yields. It was necessary to heat the mixtures initially at 150° C. and to raise the temperature slowly to 200° C. Furthermore Cuprey (4) mentioned that amides reacted with sulphamic acid to yield N-carbonyl sulphamic acids.

$$RCONH_2 + H_2NSO_3H \rightarrow RCONHSO_3H + NH_3$$

It thus seemed probable that the intermediate formed during the reaction of amides and ammonium sulphamate was of the ammonium N-carbonyl sulphamate type. In order to prove this unequivocally, seven ammonium N-carbonyl sulphamates were prepared; amides were treated with a solution of sulphuric acid in acetic anhydride and formed the amide salt of amido sulphonic acids, which with ammonium hydroxide formed ammonium N-carbonyl sulphamates.

$$2\ RCONH_2 + H_2SO_4 + (CH_3CO)_2O \rightarrow RCONHSO_3H.H_2NOCR + 2\ CH_3COOH$$
$$RCONHSO_3H.H_2NOCR + NH_4OH \rightarrow RCONHSO_3NH_4 + RCONH_2$$

When these ammonium salts were heated at 170–180° C. nitriles and ammonium bisulphate were formed.

$$RCONHSO_3NH_4 \rightarrow RCN + NH_4HSO_4$$

The yields of nitriles from ammonium N-carbonyl sulphamates were very good, varying from 90 to 95%. The results are shown in Table II.

Thus the formation of nitriles from amides and ammonium sulphamate involves a condensation of the amide with ammonium sulphamate by liberation of ammonia to yield ammonium N-carbonyl sulphamates, which decompose into nitriles and ammonium bisulphate.

$$RCONH_2 + H_2NSO_3NH_4 \rightarrow NH_3 + RCONHSO_3NH_4$$
$$RCONHSO_3NH_4 \rightarrow RCN + NH_4HSO_4$$

The mechanism indicated that secondary amides, which cannot be readily dehydrated, should produce nitriles and amines when heated with ammonium sulphamate. Three secondary amides, namely, acetanilide, *o*-acetamidobenzoic acid, and *p*-acetamidobenzoic acid were heated with ammonium sulphamate. In each case acetonitrile was isolated together with aniline, *o*-aminobenzoic acid, and *p*-aminobenzoic acid.

Ureas and Ammonium Sulphamate

Boivin and Lovecy (3) reported that guanidine was formed when urea was heated with ammonium sulphamate. It was thus of interest to determine the behavior not only of urea but also of mono- and di-substituted ureas towards ammonium sulphamate.

Urea

When urea was heated with ammonium sulphamate, guanidine and cyanuric acid were formed. The yield of guanidine varied with the temperature and time of the reaction but only slightly with the amount of ammonium sulphamate used. The results are given in Table III.

Alkylureas

It was found that methylurea and 1,3-dimethylurea reacted with ammonium sulphamate in a manner analogous to that of urea. Methylamine was isolated from the reaction mixtures.

Methyl groups had little effect on the reactivity of the urea molecule. Guanidine was isolated and not methylguanidine. The yield of guanidine varied with the temperature and time of the reaction and the amount of ammonium sulphamate used. The results are found in Tables IV and V.

Arylureas

Monophenylurea when heated with ammonium sulphamate reacted as did the alkylureas; guanidine and cyanuric acid were formed together with aniline and diphenylurea. The yield of guanidine was affected by the amount of ammonium sulphamate used but only slightly by the temperature and time of the reaction. The results are shown in Table VI.

Diphenylurea produced only aniline and no guanidine nor cyanuric acid when heated with ammonium sulphamate.

Alkoyl and Aroylureas

The effects of alkoyl and aroyl groups on the reactivity of the urea molecule were studied. It was noted that the carbonyl of an acetyl or benzoyl group was more reactive than the carbonyl group of urea. In the reactions of acetylurea and benzoylurea with ammonium sulphamate, the substituted urea decomposed to form acetamide or benzamide and hence the corresponding nitriles and cyanuric acid. The yield of guanidine was low while that of cyanuric acid was very high. The results are listed in Tables VII and VIII.

Diacetylurea when heated with ammonium sulphamate produced only acetonitrile and no guanidine nor cyanuric acid.

Salts of Carbamylsulphamate

Boivin and Lovecy (3) reported that ammonium carbamylsulphamate was formed when urea reacted with ammonium sulphamate at 140° C.

Ammonium carbamylsulphamate was prepared in a manner analogous to the preparation of ammonium N-carbonyl sulphamates previously mentioned. Urea reacted with sulphuric acid in acetic anhydride to form urea carbamylsulphamate. This viscous salt, which could not be induced to crystallize immediately, was treated with ammonium hydroxide to form ammonium carbamylsulphamate.

$$2\ H_2NCONH_2 + H_2SO_4 + (CH_3CO)_2O \rightarrow H_2NCONHSO_3H.H_2NCONH_2 + 2CH_3COOH$$

$$H_2NCONHSO_3H.H_2NCONH_2 + NH_4OH \rightarrow H_2NCONHSO_3NH_4 + H_2NCONH_2$$

When ammonium carbamylsulphamate was heated alone, guanidine and cyanuric acid were formed. The yield of guanidine was increased by the addition of ammonium sulphamate. The results are given in Table IX.

By analogy with the reactions of amides and ammonium sulphamate, or of the intermediate ammonium N-carbonyl sulphamates, it seemed that ammonium carbamylsulphamate should produce the corresponding nitrile, which

is cyanamide. It is well known that cyanamide in the presence of an ammonium salt is converted into guanidine or its trimer, melamine. Thus the formation of guanidine from ammonium carbamylsulphamate would proceed as follows.

$$H_2NCONHSO_3NH_4 \rightleftharpoons NH_4OCN + NH_4HSO_4$$
$$NH_4OCN \rightarrow HOCN + NH_3$$
$$3\ HOCN \rightleftharpoons (HOCN)_3$$
$$H_2NCONHSO_3NH_4 \rightarrow H_2NCN + NH_4HSO_4 + NH_3 \rightarrow H_2NC(NH)NH_3SO_4NH_4$$

In order to prove that the formation of guanidine does occur through the condensation of cyanic acid with ammonium sulphamate to form ammonium carbamylsulphamate, potassium, sodium, and urea carbamylsulphamates were heated alone and with ammonium sulphamate.

As expected, only cyanuric acid was isolated when these three salts were heated alone. It was necessary to heat the salts with ammonium sulphamate in order that guanidine be formed.

In view of the experimental results obtained the mechanism of the formation of guanidine occurs through the condensation of cyanic acid with ammonium sulphamate, forming ammonium carbamylsulphamate, which is converted into guanidine.

$$HOCN + H_2NSO_3NH_4 \rightarrow H_2NCONHSO_3NH_4 + NH_3 \rightarrow H_2NC(NH)NH_3SO_4NH_4$$

Salts of N-Methylcarbamylsulphamate

In order to determine why no methylguanidine was formed when methylurea and dimethylurea were heated with ammonium sulphamate, the behavior of ammonium N-methylcarbamylsulphamate was studied.

This salt heated alone produced only cyanuric acid. With ammonium sulphamate at temperatures not exceeding 230° C. methylguanidine together with traces of guanidine was isolated. At temperatures above 230° C. only guanidine and no methylguanidine was formed. The results are listed in Table X.

The fact that methylguanidine was readily formed from ammonium sulphamate and ammonium N-methylcarbamylsulphamate proves that the formation of this salt is an essential step in the production of methylguanidine from methylurea and dimethylurea. However, since methylguanidine is not isolated from the reactions of methylurea and dimethylurea, the formation of ammonium N-methylcarbamylsulphamate was prevented. The experimental conditions used favored the formation of ammonium carbamylsulphamate and hence guanidine.

Thus two opposing reactions were involved when methylurea or dimethylurea was heated with ammonium sulphamate; guanidine was formed in preference to methylguanidine.

From the study it is concluded that the formation of nitriles by the reaction of amides and ammonium sulphamate involves a condensation of the amide with ammonium sulphamate, the liberation of ammonia, and the formation of ammonium N-carbonyl sulphamates, which decompose into nitriles and ammonium bisulphate. This method of preparing nitriles is generally applicable to most amides.

The formation of guanidine from urea and substituted ureas is due to the condensation of cyanic acid with ammonium sulphamate resulting in the formation of ammonium carbamylsulphamate, which is converted into guanidine and ammonium bisulphate. Alkyl and aryl ureas produce amines and alkoyl and aroyl ureas produce nitriles in addition to guanidine and cyanuric acid.

EXPERIMENTAL

Direct Synthesis of Nitriles

In a distilling flask equipped with a short column was placed ammonium sulphamate (17.10 gm., 0.15 mole) and an amide (0.1 mole). The mixture was heated in a metal bath, the temperature of which was slowly raised from 150° C. up to 190–200° C. The liquid nitriles were collected by distillation and the solid ones by vacuum distillation or extraction with a suitable solvent. The results are shown in Table I.

TABLE I

AMIDES AND NITRILES

Amides	Nitriles	M.p., °C.	B.p., °C.	Yield, %	Calc., % N	Found, % N
X	CH_3CN		81–82	10	34.15	34.20
$C_3H_7CONH_2$	C_3H_7CN		216	65	20.3	20.38
$C_4H_9CONH_2$	C_4H_9CN		142	70	16.75	16.80
$C_4H_9CONH_2$	C_4H_9CN		129–130	80	16.75	16.81
$C_5H_{11}CONH_2$	$C_5H_{11}CN$		162	80	14.43	14.38
$C_{17}H_{35}CONH_2$	$C_{17}H_{35}CN$	41.5		92	5.28	5.30
$C_4H_8(CONH_2)_2$	$C_4H_8(CN)_2$		153/6 mm.	45	25.92	25.98
o-$CH_3C_6H_4CONH_2$	*o*-$CH_3C_6H_4CN$		201–202	75	11.96	12.0
p-$CH_3C_6H_4CONH_2$	*p*-$CH_3C_6H_4CN$	30	215–216	90	11.96	11.99
$HOC_6H_4CONH_2$	HOC_6H_4CN	98		25	11.76	11.83
$C_6H_5CH_2CONH_2$	$C_6H_5CH_2CN$		206/107 mm.	45	11.96	11.94
$C_2H_5CH(C_6H_5)CONH_2$	$C_2H_5CH(C_6H_5)CN$		107/7 mm.	80	9.65	9.7
$C_6H_5OCH_2CONH_2$	$C_6H_5OCH_2CN$		115/11 mm.	65	10.52	10.58
$C_{10}H_7CH_2CONH_2$	$C_{10}H_7CH_2CN$	33	178/12 mm.	58	8.38	8.40
$C_4H_9OCONH_2$	C_4H_9OCN		148–150	15	15.05	15.09
$C_6H_5NCONH_2$	C_6H_5NCN	51		85	26.92	26.99

X = $CH_3CONHC_6H_5$ or o-$CH_3CONHC_6H_4COOH$ or p-$CH_3CONHC_6H_4COOH$.

Preparation of Nitriles from Ammonium N-Carbonyl Sulphamates

An amide (0.1 mole) was added to cold mixture of acetic anhydride (250 ml.) and sulphuric acid (49.0 gm., 0.5 mole). The solution was cooled to −20° C. in an acetone – dry-ice bath. The bulky white solid which separated out was filtered, washed well with anhydrous ethyl ether, and dissolved in ethanol (250 ml.). The alcoholic solution was treated with ammonium hydroxide (80 ml.) and cooled. The ammonium N-carbonyl sulphamates were isolated as crystalline solids which are not described in the literature. The results are shown in Table II.

Upon the heating of these ammonium salts at 170–180° C. nitriles and ammonium bisulphate were isolated. The nitriles isolated from ammonium N-carbonyl sulphamates are given in Table II.

Ureas and Ammonium Sulphamate

The ureas (0.1 mole) and ammonium sulphamate (0.1, 0.2, 0.3 mole) were heated in the same manner as described for the amides and ammonium sulphamate. The temperature and time of the reaction were varied.

The reaction products were water leached and the filtrates were analyzed for guanidine and cyanuric acid. Guanidine was estimated as the picrate and cyanuric acid as melamine cyanurate. The results are listed in Tables III, IV, V, VI, VII, and VIII.

TABLE II

AMMONIUM N-CARBONYL SULPHAMATES AND NITRILES

Ammonium N-carbonyl sulphamates	M.p., °C.	Yield, %	Calc. % N	Calc. % SO_3	Found % N	Found % SO_3	Nitriles	Yield, %
$C_{17}H_{35}CONHSO_3NH_4$	115	90	7.37	21.05	7.39	20.98	$C_{17}H_{35}CN$	95
$C_4H_8(CONHSO_3NH_4)_2$	208	85	16.56	47.33	16.48	47.5	$C_4H_8(CN)_2$	90
$C_7H_7CONHSO_3NH_4$	140	95	12.07	34.49	12.0	34.53	C_7H_7CN	97
$C_7H_7CONHSO_3NH_4$	160	75	12.07	34.49	11.99	34.51	C_7H_7CN	95
$HOC_6H_4CONHSO_3NH_4$	143	80	11.96	34.19	11.91	34.1	HOC_6H_4CN	95
$C_6H_5CH_2CONHSO_3NH_4$	127	95	12.07	34.48	11.99	34.51	$C_6H_5CH_2CN$	85
$C_{10}H_7CH_2CONHSO_3NH_4$	157	85	9.93	28.39	9.97	28.43	$C_{10}H_7CH_2CN$	95

TABLE III

UREA AND AMMONIUM SULPHAMATE

Molar ratio H_2NCONH_2: $H_2NSO_3NH_4$	Temp., °C.	Time in minutes Total	Time in minutes Above 200° C.	Yield, % Guanidine	Yield, % Cyanuric acid
1:1	200	50	45	30.1	32.1
1:1	230	75	70	30.2	3.0
1:2	200	50	45	33.9	2.0
1:2	200	74	70	33.8	4.6
1:2	230	23	15	59.2	14.0
1:2	230	14	8	59.2	4.0
1:2	250	14	5	40.7	16.0
1:2	275	8	4	40.3	14.0
1:3	200	50	45	32.4	1.0
1:3	230	75	70	35.8	4.0

TABLE IV

METHYLUREA AND AMMONIUM SULPHAMATE

Molar ratio $CH_3NHCONH_2$: $H_2NSO_3NH_4$	Temp., °C.	Time in minutes Total	Time in minutes Above 200° C.	Yield, % Guanidine	Yield, % Cyanuric acid
1:1	250	20	10	Nil	25.6
1:2	200	65	59	8.5	Traces
1:2	210	61	48	25.4	2.3
1:2	220	45	31	27.1	4.2
1:2	230	30	13	27.1	4.2
1:2	250	14	4	28.8	4.9
1:3	250	20	10	32.2	7.0
1:3	250	30	20	49.4	4.2

TABLE V

DIMETHYLUREA AND AMMONIUM SULPHAMATE

Molar ratio $CH_3NHCONHCH_3$: $H_2NSO_3NH_4$	Temp., ° C.	Time in minutes		Yield, %	
		Total	Above 200° C.	Guanidine	Cyanuric acid
1:1	250	16	10	2.0	2.3
1:1	250	28	20	2.0	Traces
1:2	200	110	100	1.8	Traces
1:2	220	48	38	2.0	Traces
1:2	230	25	16	11.0	Traces
1:2	230	42	35	25.0	Traces
1:2	250	23	10	29.0	Traces
1:2	250	31	20	29.0	Traces
1:3	250	16	10	35.7	2.3
1:3	250	28	20	35.7	2.3

TABLE VI

MONOPHENYLUREA AND AMMONIUM SULPHAMATE

Molar ratio $C_6H_5NHCONH_2$: $H_2NSO_3NH_4$	Temp., ° C.	Time in minutes		Yield, %	
		Total	Above 200° C.	Guanidine	Cyanuric acid
1:1	230	35	20	12.5	17.0
1:2	200	180	170	Nil	Nil
1:2	230	70	60	24.0	26.0
1:2	250	23	14	24.0	26.0
1:2	275	18	4	25.0	26.5
1:3	250	25	14	30.0	15.0
1:3	275	18	4	50.0	7.0

TABLE VII

MONOACETYLUREA AND AMMONIUM SULPHAMATE

Molar ratio $CH_3CONHCONH_2$: $H_2NSO_3NH_4$	Temp., ° C.	Time in minutes		Yield, %	
		Total	Above 200° C.	Guanidine	Cyanuric acid*
1:1	230	60	25	13.0	85.0
1:2	200	120	105	23.7	75.0
1:2	230	60	25	25.1	81.0
1:2	230	75	50	25.4	79.0
1:2	250	30	10	25.1	81.0
1:2	275	45	4	17.0	50.0
1:3	230	60	25	26.2	76.0

**The method of determining cyanuric acid by the use of melamine is known to give high results.*

Salts of Carbamylsulphamate

The viscous urea salt was prepared as described by Boivin and Lovecy (3). After decanting, the salt was well washed with anhydrous ethyl ether, dissolved in ethanol (50 ml.), and anhydrous ethyl ether was added (300 ml.). The mixture was left standing overnight at room temperature. The white needle-like solid was filtered, well washed with ether, and dried *in vacuo* for two days. Pure urea carbamylsulphamate was obtained, m.p. 123° C. Yield, 30%.

TABLE VIII

MONOBENZOYLUREA AND AMMONIUM SULPHAMATE

Molar ratio $C_6H_5CONHCONH_2$: $H_2NSO_3NH_4$	Temp., ° C.	Time in minutes		Yield, %	
		Total	Above 200° C.	Guanidine	Cyanuric acid*
1:1	230	45	40	10.0	88.0
1:2	200	150	130	23.0	70.0
1:2	230	50	45	27.0	80.0
1:2	230	45	30	25.0	80.0
1:2	275	18	3	26.0	80.0
1:3	230	45	40	27.0	78.0

**The method of determining cyanuric acid by the use of melamine is known to give high results.*

Calculated for $C_2H_7O_5N_4S$: C, 12.06%; H, 3.52%; N, 28.14%; S, 16.08%. Found: C, 12.01%; H, 3.5%; N, 28.2%; S, 16.2%.

The ammonium, sodium, and potassium urea carbamylsulphamates were prepared by treating an alcoholic solution of the viscous urea salt with an aqueous solution of the appropriate hydroxide. Ammonium carbamylsulphamate was isolated, m.p. 167–168° C. (reported m.p. 167.5–168° C.). Sodium carbamylsulphamate had no definite melting point but decomposed at 220° C. Yield, 70%. Calculated for $CH_3O_4N_2S$ Na: N, 17.28%; SO_3, 49.38%. Found: N, 17.32%; SO_3, 49.41%. Potassium carbamylsulphamate had no definite melting point but decomposed at 200° C. Yield, 75%. Calculated for $CH_3O_4N_2SK$: N, 15.73%; SO_3, 44.90%. Found: N, 15.78%; SO_3, 44.80%.

The carbamylsulphamates were heated alone and with ammonium sulphamate in the same manner as described for the reactions of amides and ammonium sulphamate. The reaction products were water leached and the filtrates were analyzed for guanidine and cyanuric acid. The results obtained for ammonium carbamylsulphamate are listed in Table IX.

TABLE IX

AMMONIUM CARBAMYLSULPHAMATE

Molar ratio $H_2NCONHSO_3NH_4$: $H_2NSO_3NH_4$	Temp., ° C.	Time in minutes		Yield, %	
		Total	Above 200° C.	Guanidine	Cyanuric acid
1:0	200	25	20	Nil	50.0
1:0	230	25	20	19.0	70.0
1:0	250	18	10	35.0	35.0
1:1	200	27	20	16.0	25.0
1:1	230	18	10	49.0	11.0
1:2	230	25	20	69.0	14.0
1:2	250	25	20	97.0	2.0
1:4	230	16	10	76.0	7.0
1:4	230	28	20	80.0	7.0

Salts of N-Methylcarbamylsulphamate

Methylurea (73.0 gm., 1.0 mole) was added to a cold mixture of acetic anhydride (250 ml.) and sulphuric acid (49.0 gm., 0.5 mole). The solution

was cooled to −20° C. and the viscous methylurea salt was decanted. Crystallization was effected by dissolving the salt in ethanol (150 ml.) and adding anhydrous ethyl ether (100 ml.). The white crystalline methylurea salt was isolated, m.p. 107–108° C. Yield, 80%. Calculated for $C_4H_{11}O_5N_4S$: N, 24.67%; SO_3, 35.2%. Found: N, 24.7%; SO_3, 35.3%.

Ammonium N-methylcarbamylsulphamate was prepared by treating an alcoholic solution of the viscous methylurea salt with ammonium hydroxide (80 ml.). Pure ammonium N-methylcarbamylsulphamate was obtained, m.p. 139–140° C. with decomposition. Yield, 80%. Calculated for $C_2H_9O_4N_3S$: N, 24.56%; SO_3, 46.79%. Found: N, 24.8%; SO_3, 46.84%.

Both salts were heated alone and with ammonium sulphamate. The results for ammonium N-methylcarbamylsulphamate are shown in Table X.

TABLE X

AMMONIUM N-METHYLCARBAMYLSULPHAMATE

Molar ratio $CH_3NHCONHSO_3NH_4$: $H_2NSO_3NH_4$	Temp., ° C.	Time in minutes		Yield, %		
		Total	Above 200° C.	Methylguanidine	Guanidine	Cyanuric acid
1:0	200	29	20	Nil	Nil	92.0
1:0	230	29	20	Nil	Nil	50.0
1:0	250	30	20	Nil	Traces	40.0
1:1	200	26	20	34.0	Traces	Traces
1:2	230	26	20	85.0	Traces	Traces
1:2	250	27	20	Traces	57.0	Traces

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